**Original article / *Araştırma***

# Evaluation of serum urotensin-II levels of children with ADHD and autism spectrum disorder

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***ABSTRACT***

***Objective:*** *Urotensin-II (U-II) is one of the most vasoconstrictive substrates for the mammals. Lately, this substrate is thought to be responsible for developing of the neuropsychiatric disorders, by causing an abnormal brain blood-stream situation. Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are frequently seen disorders in childhood and their etiologies are remain unclear. This study evaluated the serum urotensin-II levels of children with ASD and ADHD and compared with healthy subjects' urotensin-II levels.* ***Methods:*** *Total of 179 children between age of 4-12, 60 of them diagnosed with ADHD and 60 of children with ASD, according to the DSM-5 criteria and both had no treatment for at least a month and 59 of healthy subjects whom they all admitted to the Ankara Pediatric Hematology-Oncology Training and Research Hospital were included. Schedule for Affective Disorders and Schizophrenia for School-Age Children, a semi-structured interview, was applied to all subjects. Venous samples of the participants were given after a-12 hours starvation. Serum U-II levels were analyzed by the use of ELISA kits. SPSS 16.0 was used for analysis and p<0.05 was accepted as significance level.* ***Results:*** *U-II levels of children with ASD were found higher than that of ADHD and healthy groups. There was also a positive correlation between U-II levels and autism behavior checklist scores.* ***Discussion:*** *Higher U-II levels and its levels' correlation with symptom severity of disorder are thought to be a responsible factor that could play a role in ASD etiology. Further studies with larger sample size could be useful to investigate the role of UII in the etiology and treatment research of ASD.* ***(Anatolian Journal of Psychiatry 2018; 19(1):80-86)***

***Keywords:*** *urotensin II, attention-deficit/hyperactivity disorder, autism spectrum disorders, oxidative stress*

# *DEHB ve otizm spektrum bozukluğu olan çocuklarda serum ürotensin-II düzeylerinin değerlendirilmesi*

***ÖZ***

***Amaç:*** *Ürotensin-II (U-II), bilinen en etkin vazokonstrüktörlerden biridir. Beyin kan akımında oluşturduğu etkilerden dolayı nöropsikiyatrik hastalıkların gelişiminde rol oynadığı düşünülmektedir. Otizm spektrum bozukluğu (OSB) ve dikkat eksikliği hiperaktivite bozukluğu (DEHB) çocukluk çağında sık görülen ve etiyolojileri halen tam olarak bilinemeyen nöropsikiyatrik hastalıklardır. Bu çalışmada OSB ve DEHB'li çocukların serum U-II düzeylerinin değerlendirilmesi ve sağlıklı kontrollerle karşılaştırılması amaçlanmıştır.* ***Yöntem:*** *Ankara Çocuk Hematoloji ve Onkoloji Eğitim ve Araştırma Hastanesi, Çocuk ve Ergen Psikiyatrisi Polikliniği'ne başvuranlar arasından, DSM-5 tanı ölçütlerine*

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*göre DEHB ve OSB tanısı konan ve en az bir aydır ilaç kullanmayan 4-12 yaşları arasında 60'ar çocuk ile sağlıklı 59 çocuk çalışmaya alınmıştır. Katılımcılara Okul Çağı Çocukları için Duygulanım Bozuklukları ve Şizofreni Görüşmesi uygulanmıştır. On iki saat açlık sonrası venöz kan örnekleri alınarak ELİSA yöntemi ile serum U-II düzeyi belirlenmiştir. Analizler için SPSS 16.0 kullanılmış, anlamlılık düzeyi p<0.05 olarak belirlenmiştir.* ***Sonuç:*** *DEHB, OSB ve kontrol grupları arasında en yüksek U-II düzeyi OSB grubunda bulunmuştur. Ayrıca OSB'li çocukların belirtilerine yönelik ölçek puanları ile serum U-II düzeyleri arasında pozitif korelasyon bulunmuştur.* ***Tartışma:*** *Kan düzeyinin yüksek olması ve belirti şiddeti ile korelasyon göstermesi, ürotensinin OSB etiyolojisinde rol oynayabileceğini düşündürmüştür. Serum U-II düzeylerinin daha geniş gruplarda değerlendirileceği çalışmalar, otizm etiyolojisi ve tedavi araştırmaları açısından yararlı olabilir.* ***(Anadolu Psikiyatri Derg 2018; 19(1):80-86)***

***Anahtar sözcükler:*** *Ürotensin-II, dikkat eksikliği hiperaktivite bozukluğu, otizm spektrum bozuklukları, oksidatif stres*

## INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that emerges in the very early periods of life and impairs the communication abilities of the affected child in social interaction, resulting in insufficient language skills and stereotypical movements accompanied by restricted areas of interest.[1] Alongside some genetic, prenatal, early postnatal, and biochemical factors that have been considered to be responsible for the etiology of ASD, it is still not thoroughly understood. For instance, only a part of all ASD cases have an identifiable factor that is thought to be playing role at the etiology.[2]The majority of ASD cases are not due to a single gene or another reason. In addition, ASD has a higher ratio of comorbidity resulting in significant economic burdens, and its frequency has actually increased as of late.[3]

Attention deficit hyperactivity disorder (ADHD) is the mostly seen neuropsychiatric disorder in childhood.[4] Inattentiveness and distractibility (difficulty completing work) are core symptoms and increased impulsivity (talking out of turn, interrupting) and impairments in executive functioning (organization, working memory) are frequently seen. Its frequency is reported as 8% to 12%.[5] Its etiology also remains unclear.[6]

The common features of ADHD and ASD have been studied in many aspects and dimensions. It is highlighted that these disorders have similar genetic and biological points and these are likely to be frequently seen in the same person.[7,8]

The role of U-II in the pathophysiology of neuropsychiatric disorders is inspiring interest in recent years. Urotensin-II (U-II) is a cyclic undecapeptide first isolated in 1969 from the caudal neurosecretory system of a fish.[9] It consists of 11 amino acids[10] and characterized by being a significantly endogenous vasoconstrictive substrate.[11] The U-II receptor acts by binding to Gq/11, one of members of the G-protein family. Stimulation of the U-II via receptor's phosphorinositide cycle causes an influx of $Ca^{+2}$ into the cells, thus increasing the levels of intracellular $Ca^{+2}$.[12] Vascular endothelial cells, the myocardium, smooth muscle cells, adrenal tissues, the thyroid, and the renal cortex are known to have U-II receptors.[13] In animal studies, U-II has been found in the central nervous system, the cerebral cortex, the amygdala, the hippocampus, the nucleus accumbens, the thalamus, and the striatum.[14-16] Studies have also revealed that U-II decreases in the bloodstream in both the frontal and temporal regions of the brain, and this situation has been considered to be one of the underlying factors impacting the etiologies of neuropsychiatric disorders.[17] Studies with rats have revealed that anxious and depressive behaviors increase after U-II injection.[18] In addition, U-II injections applied to the cerebroventricular areas of the rats have been shown to cause an increase in free oxygen radical levels.[19] Moreover, U-II has been considered to be a decreasing factor of neuronal activity in the hippocampal CA1 neurons via the Cl canals attached to the GABA-A receptors, and nitric oxide could be a possible mediator for this type of case as well.[18]

Another study conducted with dementia patients revealed that serum U-II levels and the thickness of the carotid artery intima were higher in cases of vascular dementia than with Alzheimer's and the control. Furthermore, there was no reported association between Alzheimer's and U-II levels.[20] These findings indicate that U-II could play a role in vascular dementia's etiology via severe vasoconstriction. U-II is also an important molecule for understanding the brain's blood supply, as well as oxidative and immunological mechanisms.[20,21]

Oxidative and immunologic mechanisms are also subjected to playing role in the etiology of ADHD and ASD.[22,23] In this context, it worths to analyze that if U-II levels have an effect on microcirculation and this might have an important aspect in the etiology of ASD or ADHD.

There is still no study concerning U-II levels in children with ADHD and ASD in national or international aspects.

Therefore this study aims:
- to evaluate serum U-II levels of children with ADHD or ASD,
- to analyze autism severity, problematic behaviors and their association with U-II levels and demographic features,
- to determine ADHD symptom severity and analyze should any correlation between U-II levels and sociodemographic features.

## METHODS

Total of 179 cases aged from 4 to 12 and admitted to the Ankara Pediatric Hematology-Oncology Training and Research Hospital between September 1st 2016 and November 1st 2016 were included in this study. The sample comprised 60 children diagnosed with ADHD, 60 children diagnosed with ASD according to DSM-5 criteria and 59 healthy children. All participants and their parents were informed about the study. Written and verbal consents were taken prior to testing. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version was applied to our clinical sample. Gökler et al. studied the reliability and validity of Turkish version.[24]

The children aged between 6 and 12 were applied to Wechsler intelligence scale for children-revised (WISC-R) and the developmental stages of children younger than 6 years were assessed by using Denver Developmental Screening Test-II. The presence of mental retardation or developmental delay, comorbidity, chronic systemic disorders (neurological, allergic or endocrinological) and having any medication in last month were exclusion criteria.

The parents and teachers of children diagnosed with ADHD fulfilled Conners' rating scales. On the one hand, autism behavior control checklist and problematic behavior checklist were filled by parents of children diagnosed with ASD and childhood autism checklist scale was applied to all autistic children by the interviewer.

Venous samples of 10 cc were obtained from participants and extracted after 15 minutes; they were then centrifuged for 5-10 minutes at 3000 rpm and stored at -20$^0$C. All samples were analyzed with the ELISA method which is an analytic biochemistry assay that is used to detect and quantify the presence of a substance. After an overnight starvation, samples were collected from the participants at the period of 08.00-09.00 a.m.

This study was approved by local ethical committee. The serum U-II kit was provided by the Scientific Research Coordination Unit of our hospital.

### Instruments

***Conners' Parent Rating Scale-Revised Long Form:*** It is a parent reported scale consists of 80 items and used to assess behavioral problems and severity of ADHD symptoms of children aged from 3 to 17.[25] Translation, validity and reliability of the Turkish version of the scales were performed.[26]

**Conners' Teacher Rating Scale-Revised Long Form:** This is a scale fulfilled by teachers toassess behavioral problems and severity of ADHD symptoms of children aged from 3 to 17.[25] Translation, validity and reliability of the Turkish version of the scales were performed.[27]

***Problematic Behavior Checklist (Aberrant Behavior Checklist) (PBC):*** This is a scale used for determining the severity of behavioral problems of children with autism. Parents score the problematic behavior on a five-point Likert scale.[28,29] Validity and reliability studies for a Turkish sample were completed by Karabekiroglu and Arman.[30]

***Childhood Autism Rating Scale (CARS):*** It is an autism behavior rating scale which consists of 15-items and used for diagnosis and determination of severity of autism. Each item is score from 1 to 4.[31] The total score should be minimum 30 if the child has autism.[32,33] Validity and reliability studies for a Turkish sample were completed.[34]

***Autism Behavior Checklist (ABC):*** The ABC was developed by Krug.[35] This checklist consists of 57 items in five categories. It is used by clinicians to quantify behaviors associated with autism. Turkish reliability and validity studies have been conducted.[36] The scale's cut-off point is 39.

### Statistical analysis

SPSS 16.0 was used for the analyses. The normality of the variables was tested via the Shapiro-Wilk test. To compare the variables among the groups (ASD, ADHD, and the control), the Kruskal-Wallis test was used, and with the Bonferroni correction, $p<0.0167$ was accepted as the significance level. Mann- Whitney U test was used for comparing the differences between independent groups and $p<0.05$

was accepted as the significance level. Chi-squared test was used to compare the categorical variables. Spearman's test was used for determining the correlation of the variables, and p<0.05 was accepted as the significance level.

## RESULTS

The sociodemographic and clinical features of the groups are summarized in Table 1. There was no significant difference found between the ASD, ADHD, and control groups in terms of both the mothers' and fathers' ages and their education levels. The mean ages of the groups, on the other hand, was significantly different (p=0.048). According to binary comparisons, the difference was a result of the higher age distribution of children with ASD compared to that of the control group (p=0.014; p<0.0167) (Table 1).

**Table 1.** Demographics, clinical features and urotensin II levels of the groups

| | ASD (n=60) | ADHD (n=60) | Control (n=59) | p |
|---|---|---|---|---|
| Age (month) | 124.2±10.4 | 121.6±9.4 | 118.6±9.2 | 0.048* |
| Gender (F/M) | 16/44 | 17/43 | 19/40 | 0.793** |
| Mother age (year) | 32.8±5.1 | 33.1±4.4 | 33.5±4.1 | 0.559* |
| Mother education (year) | 10.3±3.4 | 10.9±3.7 | 11.0±3.5 | 0.441* |
| Father age (year) | 36.5±5.8 | 37.1±4.9 | 36.9±5.5 | 0.584* |
| Father education (year) | 11.7±3.2 | 11.1±3.3 | 11.2±3.0 | 0.464* |
| Conner's Parent Scale | | 39.8±2.7 | | |
| Conner's Teacher Scale | | 42.2±4.1 | | |
| ABC | 65.3±22.0 | | | |
| PBCL | 51.4±14.2 | | | |
| CARS | 36.7±4.4 | | | |
| U-II (pg/mL) | 6.9±1.5 | 6.2±1.6 | 6.5±1.9 | 0.027* |

*ASD: Autism Spectrum Disorder; ADHD: Attention Deficit Hyperactivity Disorder; ABC: Autism Behavior Checklist; PBCL: Problematic Behavior Controls Checklist; CARS: Childhood Autism Rating Scale.*
** Kruskal-Wallis Test*

Median U-II levels were 6.9±1.5 pg/ml, 6.2±1.6 pg/ml and 6.5±1.9 pg/ml for those with autism, those with ADHD, and healthy subjects, respectively. There was a significant difference among the groups in terms of U-II levels (p=0.027). This significance was due to the comparison between U-II levels of subjects with ASD and ADHD (p=0.007; p<0.0167).

Correlation analysis of the variables revealed a positive relationship between U-II levels and ABC scores (r=0.29; p=0.023) and CARS scores (r=0.26; p=0.042). There was also a negative correlation between age and CARS scores (r=-0.42; p=0.001) (Table 2). Other correlations found to be significant were the positive relationships between CARS and ABC scores (r=0.54; p<0.005) and CARS and PBC scores (r=0.29; p=0.023) (Table 2). Another positive correlation detected was that between Conners' Parents and Teacher Scales (r=0.26; p=0.049). There was, however, no correlation between U-II levels and Conner's Parents and Teacher Scales (p>0.05).

**Table 2.** Correlation between urotensin II levels and ABC and CARS scores

| | ABC | CARS |
|---|---|---|
| Urotensin II | 0.293*<br>0.023 | 0.263*<br>0.042 |
| ABC | 1 | 0.544**<br>0.000 |

**: 0.05 (correlation is significant at the 0.05 level (2-tailed)*
***: 0.01 (correlation is significant at the 0.01 level (2-tailed)*
**/** Spearman*

## DISCUSSION

The serum U-II levels of children with ADHD or ASD were evaluated in this study. The most prominent finding was the higher serum U-II levels of children with ASD than those with ADHD. Moreover, there was a positive correlation between serum U-II levels and CARS and

and ABC scales when evaluating the severity of ASD. On the other hand, there was no significance between ADHD and healthy subjects and also between ASD and healthy subjects in terms of their serum U-II levels. Additionally, there was no correlation between Conners' scales scores and U-II levels in the ADHD group. All of these findings point to the fact that higher serum U-II levels might be associated with ASD. Interestingly, similar results were not noted in other studies reporting on ASD in the literature.

A study conducted with rats revealed that U-II has a potential effect on the central nervous system via different second messengers.[20]In a similar context, U-II might have different effects on the various regions of brain, and because of this variability, U-II could play a role in the etiologies of different neuropsychiatric disorders.

In a study conducted on Turkish subjects with schizophrenia, serum U-II levels were reported as higher in the patients than they were in the controls and the elevation of U-II was claimed to cause increased reactive oxygen species in the brain.[17] Another study showed that blood flow of frontal and temporal regions decrease in schizophrenia.[37] As U-II is one of the most potent vasoconstrictors, higher U-II level is suggested to be responsible for decreased blood flow and brain volume in schizophrenia patients.[38]

Oxidative stress that is determined as damage to cellular tissue caused by free radicals has been implicated in psychiatric disorders such as schizophrenia,[39,40] depression,[41] bipolar disorder[42] and Alzheimer's disease.[43] Although oxidetive stress is thought to be a common factor in the etiology of psychiatric disorders, pathophysiological mechanisms are still unclear. But it is known that intracerebroventricular injection of U-II caused an increase of reactive oxygen species[44] in brains of the rats. Thereby, U-II levels may be associated with oxidative parameters and neuronal damage in the etiopathogenesis of psychiatric disorders.

There is also studies reporting the role of oxidetive stress in ASD.[23,45] In addition, the studies sign a mounting evidence of relation between immune dysregulation and ASD.[46] Immune dysregulation/inflammation, oxidative stress and toxicant exposures are the most related areas with ASD in recent years.[47] There are studies suggesting that immune dysregulation and neuroinflammation may lead damage in brain tissue and affect growth and structure of neurons.[48]

This study is the first to evaluate U-II levels in children with ASD and ADHD in comparison with a control group. Our findings seem to point to the possible role of U-II in the etiology of ASD. However, there are some limitations that may have affected the findings. First, this study did not include a long-term follow-up period. As another limitation, patients were included in the study from one specific center, and this led to a relatively small sample size. Additionally, participants with comorbid disorders were excluded. Furthermore, the participants were not matched according to ages. Nevertheless, since there was no correlation between U-II levels and age, unevenly distributed ages may not be a conflict or limiting issue.

In terms of the advantages of this approach, evaluating all participants via semi-structured clinical interviews in conjunction with the presence of a control group were valuable contributions of this study. Still, there is a necessity for evaluating the function of U-II in the etiology of ASD with larger samples designed with longer evaluation periods. Studies regarding U-II levels and its possible role in ASD etiology conducted with larger samples and different age groups, along with patients diagnosed with ADHD, a common comorbidity of ASD could be fundamental to understanding the underlying mechanisms of these disorders.

***Yazarların katkıları:*** *Ç.U.: Çalışmanın tasarlanması, literatür araştırması, istatistiksel analiz ve yorumlama, makalenin yazılması; Ö.Ü.: Çalışmanın danışmanlığı ve planlanması, verilerin yorumlanması, makalenin yazılması; M.S.: Çalışmanın projelendirilmesi ve yürütülmesi, materyalin toplanması, literatür araştırması, makalenin yazılması; E.S.: Çalışmanın planlanması, yöntem ve hizmet desteği, biyokimyasal ölçüm ve analizler, makalenin yazılması; G.D.: Çalışmanın planlanması, yöntem ve hizmet desteği, biyokimyasal ölçüm ve analizler, makalenin yazılması, E.S.: Sorumlu yazar, yöntem ve hizmet desteği, makalenin yazılması.*

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