

SERUM TUMOR NECROSIS FACTOR-LIKE WEAK INDUCER OF APOPTOSIS (TWEAK) LEVELS ARE DECREASED IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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received: 28.12.2020;

revised: 15.4.2021;

accepted: 16.5.2021

SUMMARY

Introduction: There has been no study in the literature evaluating serum tumor necrosis factor-like weak inducer of apoptosis (TWEAK) levels in attention-deficit/hyperactivity disorder (ADHD). Therefore, we performed the present study to specifically measure serum TWEAK levels to see whether or not its eventual alterations might have an etiopathogenetic significance in children with ADHD.

Subjects and methods: A total of 49 treatment-naïve children with ADHD and 39 healthy controls were included in the present study. The severities of ADHD and conduct disorder symptoms were assessed via parent- and teacher-rated questionnaires. Venous blood samples were collected, and serum TWEAK levels were measured.

Results: Serum TWEAK levels of the ADHD group were significantly lower than the control group.

Conclusions: This study shows that ADHD patients have decreased serum TWEAK levels, suggesting a possible involvement of TWEAK in the etiopathogenesis of ADHD.

Key words: attention-deficit/hyperactivity disorder – ADHD – cytokine - TWEAK

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood neurodevelopmental disorder with prevalence is 12.4% in a multicenter nationwide study in Turkey (Ercan et al. 2019). Genetic and environmental factors are involved in the etiology of ADHD. Genetic factors play a major role. However, the precise etiopathogenesis of ADHD is not completely defined (Thapar et al. 2013). Neuroimaging, cognition, and biochemical studies have delineated ADHD as a heterogeneous disorder with multifactorial causation (Faraone et al. 2014, Işık et al. 2018, Leffa et al. 2018, Thapar et al. 2013). The inflammatory processes have been increasingly explored among the several mechanisms that predispose to the ADHD phenotype (Dunn et al. 2019, Leffa et al. 2018).

Recently, it has been implied that there is a relationship between impaired immune system and ADHD (Dunn et al. 2019, Leffa et al. 2018). Immune mediators have been well established for their interaction with the metabolism of monoamines, synaptic plasticity, neurocircuits, and neuroendocrine function (Haroon et al. 2012). Indeed, in many psychiatric disorders, including ADHD, cytokines are now thought to be inflammatory biomarkers. There is recent evidence that patients with ADHD have higher circulating cytokine concentrations than controls, suggesting that inflammation may play a part in ADHD pathogenesis (Anand et al. 2017, Darwish et al. 2019, Donfrancesco et al. 2016, O'Shea et al. 2014). Tumor Necrosis Factor (TNF)-alpha is one of the most widely investigated inflammatory mediators owing

to its key role in modulation of innate immunity, which involves macrophage-mediated cytotoxicity regulation by pro-apoptotic signaling (Goetz et al. 2004). TNF superfamily members are a diverse group of molecules that act as main TNF-alpha regulator mediators (Tansey & Szymkowski 2009).

In the TNF family, the cytokine TNF-like weak inducer of apoptosis (TWEAK) is a secreted ligand and exists in membrane-bound and soluble variant forms (Chicheportiche et al. 1997). The latter can be evaluated in serum to represent the overall TWEAK pool concentrations. TWEAK includes a variety of biological impacts by binding to its receptor fibroblast growth factor-inducible 14 (Fn14), including tissue repair-related procedures, such as cell proliferation, cell migration, and angiogenesis (Arana et al. 2014, Zhu et al. 2018). TWEAK reduces the shift from innate to adaptive T helper 1 immune response, suppressing pro-inflammatory cytokines like interleukin (IL)-12 and interferon-gamma, and counterbalancing TNF-alpha activity (Maecker et al. 2005). Previous research has established that TWEAK may play an important role in the etiopathogenesis of a number of mental disorders such as bipolar disorder (Barbosa et al. 2017, Cingi Yirün et al. 2017), schizophrenia (Tatlidil Yaylaci et al. 2015), and crack cocaine dependence (Levandowski et al. 2014). In crack cocaine dependence and bipolar disorder studies (Cingi Yirün et al. 2017, Levandowski et al. 2014), circulating TWEAK levels were lower in the patient group than in the controls. In contrast, in the other bipolar study, plasma TWEAK concentrations were higher in the bipolar disorder group than in controls (Barbosa et al. 2017).

However, to our knowledge, serum TWEAK concentrations have not been previously evaluated in patients with ADHD and the relationship between circulating TWEAK concentrations and ADHD symptom severity was not examined. In the present research, we evaluated serum TWEAK concentrations in ADHD patients and examined whether TWEAK concentrations are linked to the severity of the ADHD symptom. Based on available information about inflammatory changes in ADHD, we assumed that TWEAK concentrations would be lower in ADHD patients in view of the suppressive impacts of TWEAK on pro-inflammatory mechanisms.

SUBJECTS AND METHODS

Subjects

This cross-sectional study was performed in Suleyman Demirel University (SDU) Medical Faculty. The inclusion criteria were: (1) an ADHD diagnosis; (2) treatment-naive condition; and (3) age 8-12 years. The exclusion criteria were: (1) the presence of a physical/neurological/metabolic disease (e.g., cardiovascular disorders, epilepsy, diabetes mellitus, etc.); (2) recent infection or vaccination; (3) comorbid intellectual disability, schizophrenia, bipolar disorder, autism spectrum disorder (ASD), and substance abuse; (4) smoking; (5) history of taking psychotropic medications and any history of anti-inflammatory drugs in the previous one month. The Schedule for Affective Disorders

and Schizophrenia for School-Age Children - Present and Lifetime Version (KSADS-PL) was administered to the patient group to support ADHD diagnosis and to exclude comorbid psychiatric disorders (Gokler et al. 2004). Patients with ASD, language delays, and learning disabilities were excluded from the research by clinical evaluation. The control group was comprised of unrelated healthy volunteers in the same age group. For the control group that did not fulfill ADHD criteria and had no history of other mental, neurological or metabolic diseases, the same exclusion criteria were performed. All the procedures for the research were consistent with the Helsinki Declaration and local laws and regulations. SDU Medical Faculty Ethics Committee assessed and endorsed the research protocol.

Diagnostic and symptom assessment

Both the target child and a parent were interviewed by a child psychiatrist using the K-SADS-PL (Gokler et al. 2004), and the diagnoses of ADHD were made based on the DSM-5 criteria. The Turgay DSM-IV- Based Child and Adolescent Behavioral Disorders Screening and Rating Scale (T-DSM-IV-S) (Ercan et al. 2001, Turgay 1994) and the Strengths and Difficulties Questionnaire (Goodman et al. 2000, Güvenir et al. 2008) were administered to the parents of the participants. The teachers of the participants completed the T-DSM-IV-S.

Table 1. Demographic and clinical characteristics of children with ADHD and controls

	ADHD (n=49)	Controls (n=39)	t/z/x ²	p
Age, years	9.7±1.4	9.8±1.5	-0.284 ^a	0.777
Sex, male/female	37/12	24/15	1.993 ^c	0.158
BMI Percentile	63.7±28.8	62.6±29.9	0.173 ^a	0.863
T-DSM-IV-S: Parent				
AD	18.8±5.1	4.7±3	-7.792 ^b	<0.001
HA/I	16.1±6.3	4.2±3.4	-7.229 ^b	<0.001
OD	13.9±6.1	5.1±3.9	-6.290 ^b	<0.001
CD	3.6±3.7	0.4±1	-5.338 ^b	<0.001
SDQ: Parent				
Emotional Problems	3.8±2.3	2±1.5	-3.812 ^b	<0.001
Conduct Problems	3.6±2.1	1.1±0.9	-5.585 ^b	<0.001
Hyperactivity	7.3±1.8	3.1±1.7	-7.284 ^b	<0.001
Peer Problems	3.7±1.7	2.3±1.6	-3.665 ^b	<0.001
Prosocial Behavior	7.3±2.2	8.5±1.3	-2.768 ^b	0.006
Total Difficulties	18.6±5.2	8.5±3.9	-7.101 ^b	<0.001
T-DSM-IV-S: Teacher				
AD	17±5.7	4.5±3.3	-7.448 ^b	<0.001
HA/I	13.8±8.4	2.3±1.7	-6.318 ^b	<0.001
OD	10.2±7.1	2.4±2.3	-5.533 ^b	<0.001
CD	4.1±5.5	0.2±0.6	-5.008 ^b	<0.001

ADHD - Attention-deficit/ hyperactivity disorder; T-DSM-IV-S - Turgay DSM IV - Based Child and Adolescent Behavioral Disorders Screening and Rating Scale; AD - Attention-Deficit; HA/I - Hyperactivity-Impulsivity; OD - Oppositional Defiant Behavior; CD - Conduct Disorder; SDQ - Strengths and Difficulties Questionnaire

^aStudent t-test; ^bMann-Whitney U test; ^cChi-square test

Blood samples

Patients and controls venous blood samples were taken between 8:00 and 10:00 a.m. following a 12-hour fast. The blood samples were centrifuged and the serum kept at -80°C until assayed. TWEAK serum concentrations have been determined in accordance with the procedures of the manufacturer using the Elabscience Instant ELISA kit (Ref: E-EL-H3651, Lot: PULNRMM2QN). Serum TWEAK concentrations were recorded in pg/ml.

Statistical Analysis

Statistical analyses have been carried out with the statistical software SPSS 20.0. The Kolmogorov – Smirnov test was used to assess the distribution of the parameters. The chi-square test was used to compare the patients' and controls' sex distribution. The patients' and controls' ages and BMI percentile were compared with the independent samples t-test. The Mann-Whitney U test used to compare psychometric test scores and TWEAK levels between groups due to the abnormal distributions of the psychometric test scores and TWEAK levels. To analyze the correlations between clinical psychiatric test scores and serum TWEAK levels, Spearman rank correlation coefficient

was used. The significance level was recognized as p -value less than 0.05 (two-tailed).

RESULTS

Table 1 provides the demographic and clinical characteristics of ADHD children and controls. There were 49 patients (37 males, 12 females) in the ADHD group and 39 (24 males, 15 females) in the control group, with mean ages of 9.7 ± 1.4 and 9.8 ± 1.5 years, respectively. There were no significant differences between groups in terms of age, sex and BMI percentile. Children in the ADHD group had significantly higher scores on all subscales of parent and teacher-rated T-DSM-IV-S and parent-rated SDQ (SDQ: P) than the control group, except SDQ: P-Prosocial Behavior.

Mean TWEAK concentrations (pg/mL) were 2.5 ± 0.9 and 3.8 ± 1.8 for patients with ADHD and comparison subjects, respectively. Serum TWEAK concentrations were significantly lower in the ADHD than in the control ($z=-3.818$, $p<0.001$). Analyses descriptions are shown in table 2 and figure 1. Relationships between serum TWEAK concentrations and subscale scores of the SDQ: P and the parent and teacher-rated T-DSM-IV-S were assessed in the ADHD group. The serum TWEAK concentrations were not associated with these questionnaire scores.

Table 2. Serum TWEAK levels of children with ADHD and healthy controls

	ADHD (n=49)	Controls (n=39)	Mann – Whitney U	
			z	p
TWEAK (pg/mL)	2.5 ± 0.9	3.8 ± 1.8	-3.818	<0.001

TWEAK - TNF-related weak inducer of apoptosis; ADHD - attention-deficit/hyperactivity disorder

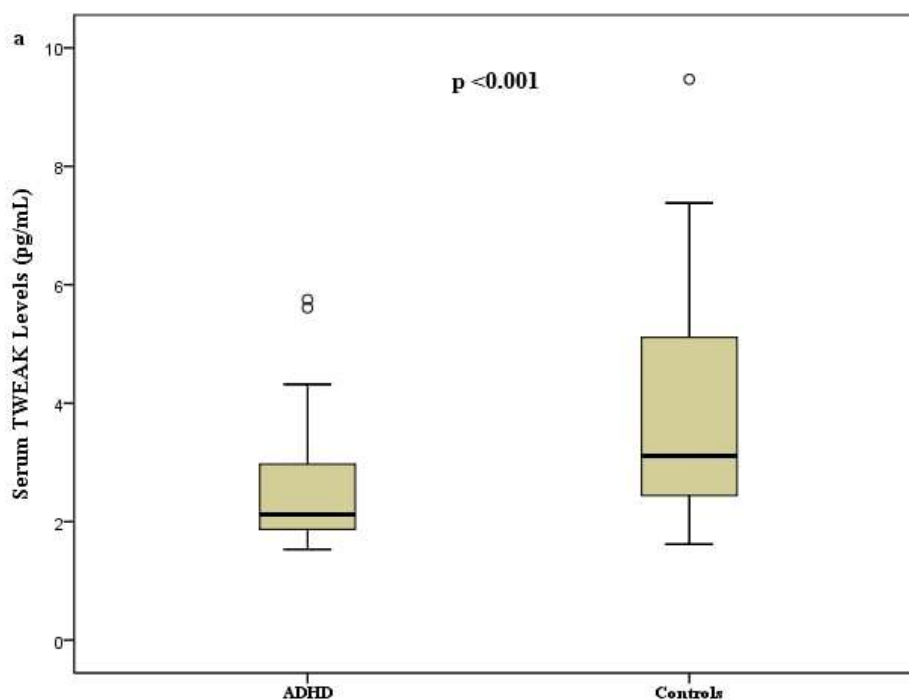


Figure 1. Box plots representing the distribution of serum TWEAK levels in ADHD and controls. ADHD: attention-deficit/hyperactivity disorder

DISCUSSION

The present research explored whether serum TWEAK concentrations are related to ADHD in childhood. The findings suggested that children with ADHD had lower serum TWEAK concentrations than controls. However, there were no significant correlations between serum TWEAK concentrations and ADHD symptom severity. These findings indicate that serum TWEAK concentrations may be related to ADHD etiopathogenesis, regardless of ADHD symptom severity.

To our knowledge, no previous studies had investigated the relationship between ADHD and TWEAK levels. To date, circulating TWEAK concentrations have only been investigated in a small number of mental disorders such as schizophrenia, bipolar disorder, and crack cocaine dependence (Barbosa et al. 2017, Cingi Yürün et al. 2017, Levandowski et al. 2014, Tatlidil Yaylaci et al. 2015). In the schizophrenia study, no significant difference was determined between the circulating TWEAK concentrations of patients and controls, but in this study, the authors showed that TWEAK concentrations of men with schizophrenia were significantly lower than controls (Tatlidil Yaylaci et al. 2015). Regarding bipolar disorder, Barbosa et al. demonstrated a link between higher TWEAK concentrations and bipolar disorder (Barbosa et al. 2017). However, the data are not universal and Cingi Yürün et al. reported significantly lower TWEAK concentrations in bipolar disorder group in either the manic episode or remission group than in the control group (Cingi Yürün et al. 2017). Lower blood TWEAK concentrations have been also reported in patients with crack cocaine-dependent women with a history of early life stress and TWEAK has been suggested as an independent diagnosis marker for crack cocaine dependence (Levandowski et al. 2014). Consistent with the results of bipolar disorder and crack cocaine dependence studies, our findings showed that children with ADHD have lower serum TWEAK concentrations than the controls. Among our findings, lower TWEAK concentrations indicate a pro-inflammatory trend in patients with ADHD as TWEAK is a molecule that balances TNF activity through the suppression of pro-inflammatory cytokine, including interferon-gamma and interleukin-12 (Maecker et al. 2005). Decreased TWEAK concentrations, in turn, could mitigate suppression and enhance the production of pro-inflammatory cytokines, thus contributing to the pro-inflammatory tendency (Arana et al. 2014, Chicheportiche et al. 1997, Maecker et al. 2005). Lower TWEAK concentrations in ADHD patients compared to controls in the present research lead to proof of inflammatory system changes in patients with ADHD (Anand et al. 2017, Darwish et al. 2019, Dunn et al. 2019, Verlaet et al. 2019).

In this study, we also examined the correlations between TWEAK concentrations and ADHD symptom severity. We were unable to identify relationships

between serum TWEAK levels and psychological test scores. Previous studies have investigated the correlation between circulating cytokine levels and ADHD symptoms. Oades et al. (2010) reported a positive correlation between enhanced IL-13 and IL-16 concentrations and symptoms of ADHD. IL-13 concentrations were correlated with the inattention symptoms, whereas enhanced IL-16 concentrations were correlated with the hyperactive-impulsive symptoms and motor activity (Oades et al. 2010). In another study, the authors demonstrated that the decrease in cytokine levels after 8 weeks of supplementation treatment with omega-3 fatty acids was correlated with significant improvement in the Conners questionnaire scores (Hariri et al. 2012). In a recent two study, the authors found no significant correlation between circulating cytokine levels and Conners scale scores (Corominas-Roso et al. 2017, Darwish et al. 2019). To the best of our knowledge, no previous study has examined the correlation between serum TWEAK concentrations and ADHD symptom severity; thus, it is currently unclear why in this research, serum TWEAK levels were not correlated with the subscale scores of the SDQ: P (conduct problems, emotional problems, hyperactivity, peer problems, and prosocial behavior) and the parent and teacher-rated T-DSM-IV-S (attention-deficit, hyperactivity-impulsivity, oppositional defiant behavior, and conduct disorder). Therefore, the correlation between TWEAK concentrations and the ADHD symptom severity may be made clear in future research.

The empirical results reported herein should be considered in light of some strengths and limitations. The inclusion of only drug-naïve patients and the exclusion of patients with medical conditions such as major physical/neurological/metabolic/ inflammatory diseases can be considered as the strength of the study. However, current research has some limitations. First, the cross-sectional design precludes any causal inference. Second, only serum TWEAK concentrations have been evaluated. For further verification, measurements of TWEAK mRNA and Fn14 expression might be needed. Finally, no evaluation has been made of some possibly confusing factors, such as socioeconomic status and other environmental factors, which must be monitored in future studies. When we look at these aspects, our research might be seen as preliminary research.

CONCLUSION

In conclusion, to the best of our knowledge, this is the first study to investigate the serum TWEAK levels in children with ADHD. We detected a decrease in serum TWEAK concentrations in drug-naïve children with ADHD compared to controls. These results demonstrate that TWEAK may play a significant role in ADHD etiopathogenesis. Prospective studies with a larger population will increase our knowledge related to the relationship between TWEAK and ADHD.

Acknowledgements: None.

Conflict of interest: None to declare.

Contribution of individual authors:

Ümit Işık: conceptualization, data curation, formal analysis, investigation, methodology, visualization, project administration, supervision, writing - review & editing.

Faruk Kılıç: conceptualization, investigation, methodology, visualization, writing - original draft.

Arif Demirdaş & Evrim Aktepe: investigation, methodology, writing - review & editing.

Pinar Aydoğan Avsar: conceptualization, data curation, investigation, methodology, visualization, writing - original draft.

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