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Title: Evaluation of Supar Levels in Attention Deficit and Hyperactivity Disorder Etiopathogenesis

Running Title: Supar Levels in ADHD

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ABSTRACT

Objective: Although a strong inflammatory basis has been demonstrated, the pathophysiology of ADHD (Attentıon Deficit Hyperactivity Disorder) has not been defined clearly. The aim of this study was to investigate whether soluble urokinase plasminogen activator receptor (suPAR), one of the inflammatory disruptor, play a role in the etiology of ADHD.

Methods: The study population comprised aged 7-13 years 50 patients, diagnosed ADHD with according to the DSM-5, without any chronic or another psychiatric disease, and 25 healhty controls. Parents of the children in the study group completed the Conners' Parent Rating Scale-Revised Short (CPRS-RS) and the teachers completed the Conners' Teacher Rating Scale-Revised Short (CTRS-RS). ELISA kits were used to measure suPAR levels in plasma samples.

Results: The mean plasma suPAR levels of ADHD patients were 2.92±1.74 ng/ml, the controls suPAR levels were 2.54±1.05 ng/ml and there was no significant difference between ADHD and the controls (Z=0.084, p=0.933) suPAR levels. No correlation was found between plasma suPAR levels and ADHD severity which assessed by Conner's parent and teacher scales.

Conclusion: The role of inflammatory systems and mediators in ADHD was emphasized in many studies and it was obtained many important data on the ADHD etiopathology. However we found no significant relation between ADHD and suPAR levels, further research is needed with large samples.

Keywords: suPAR, ADHD, inflammation, child

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Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder with complex etiology; genetic, biological and environmental factors (pre-postnatal risks, environmental toxins) have all been considered as potential risk factors (1). Evidence is growing that inflammation plays a role in the etiology of ADHD (2). Studies have shown that infections during pregnancy, at birth or in early childhood and chronic inflammatory diseases in childhood, increase the risk of ADHD (3).

In recent studies, investigating the etiology of ADHD, the relationship between ADHD and polymorphism in proinflammatory genes has been emphasized (4). It has been reported that inflammatory mediator levels are higher in patients with ADHD compared to healthy control groups (5). Inflammatory mediators (cytokines) have also been reported to play an important role in tryptophan metabolism and dopaminergic pathways in the brain, which are also implicated in ADHD. Alterations in pro-inflammatory and anti-inflammatory cytokines may be influential in the pathogenesis of ADHD (5). Also it has shown that administration of cytokines like interleukin-1β (IL-1β), interleukin-2 (IL-2), and interleukin-6 (IL-6) can cause neurotransmission changes similar to those seen in ADHD such as increased norepinephrine and reduced dopamine levels in studies with rodents (6).

It is known that protein kinase activity (PKA), which controls inflammatory responses in the brain, controls the expression of some important cytokines such as IL-6 and also induces

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the production of the urokinase plasminogen activator receptor (uPAR) which is known to play a critical role in brain development (5,7).

When brain damage occurs, PKA is weakened, and IL-6 production, an antiinflammatory cytokine, is increased (8). PKA inhibition and elevated levels of IL-6 have been shown to cause ADHD, leading to hypocampal neuronal death and neuronal differentiation (9).

Soluble urokinase plasminogen activator receptor (suPAR), the soluble form of uPAR, has emerged as a valuable indicator of the activation state of the immune system. suPAR molecule is involved in various immunological functions such as cell adhesion, migration, differentiation, proliferation and angiogenesis (10). SuPAR, a proinflammatory molecule, and its relationship with psychiatric illnesses have been the subject of many studies, and the role of suPAR in psychiatric diseases has not yet been fully elucidated (11-13). SuPAR levels in schizophrenic, depressed and suicide attempted patients were found higher than in healthy control groups (12,13).

Although there are studies in the literature regarding the relationship between PKA, IL-6 and ADHD development, there is no study investigating the relationship between suPAR and ADHD. Based on this information, this study aims to investigate the relationship between ADHD and the suPAR molecule, which is a stabilizing inflammatory marker, and to contribute to the etiopathogenesis of ADHD and to gain a new perspective on treatment methods.

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Methods

Participants

Subjects were recruited from the Outpatient Clinic for Child and Adolescent Psychiatry Department of Erciyes University in Kayseri. Treatment-naive, 50 children (13 girls, 37 boys) aged 7-13, with a diagnosis of the ADHD according to the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) were enrolled in this study. Exclusion criteria included the presence of neurological, metabolic and endocrine diseases, acute or chronic infections, smoking, psychiatric diagnosis excepting conduct disorder, oppositional defiant disorder, enuresis and encopresis. The control group consisted of 25 (11 girls, 14 boys) unrelated healthy volunteers aged 7-13, who were not affected by a major physical/neurological illness or a psychiatric disorder, neurological, metabolic and endocrine diseases, acute or chronic infections.

The socio-demographic characteristics of the children and adolescents included in the study were assessed using the semi-structured sociodemographic information form prepared by the researcher. All children were interviewed using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) by a child and adolescent psychiatrist (14,15).

The diagnoses of ADHD were made according to the DSM-5 criteria. Parents completed the Conners' Parent Rating Scale (CPRS) and teachers completed the Conners' Teacher Rating Scale (CTRS) (16-19). The treatment of the patients was arranged after the completion of the research protocol.

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This study was approved by the Erciyes University Medical Faculty local ethics committee with the number 2017/129.

Materials

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

This scale was developed by Kaufman et al. (15) after publication of DSM-IV in 1994. Turkish validation and reliability studies were performed by Gökler et al. in 2004 (14). K-SADS-PL allows screening of more than 20 different psychiatric disorders.

Conners' Parent Rating Scale (CPRS)

The CPRS consists of 48 items in total and consists of sub-tests questioning psychopathology. These sub-tests question attention deficiency and hyperactivity, behavioral difficulties and anxiety symptoms. Turkish version of CPRS, validity and reliability study was done by Dereboy et al (20).

Evaluation of SUPAR levels

Blood samples

Venous blood samples of patients and controls were drawn from an antecubital vein between 8:00 and 09:00 a.m. after an overnight fast. Blood samples in anticoagulated tubes were centrifuged for 10 minutes at 4000 rpm and the plasma was stored at −80 °C until assayed. Serum levels of suPAR were measured using commercial enzyme-linked immunosorbent assay

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(ELISA) kits following the protocols of the manufacturers (Biovendor Research and Diagnostic Products, Czech Republic) (Sensitivity: 5.1, assay range : 7.8-500 pg/ml).

Statistical Analysis

We used SPSS 20 (Statistical Program for Social Sciences for Windows) package program for the statistical analysis**.** The normal distribution of continuous variables with two groups was evaluated by the Shapiro Wilk Test. The Independent Sample t test was used to compare the variables with normal distribution and the Mann-Whitney U test was used to compare the variables with non normal distribution between the groups. The Pearson Chi square test was used to compare the categorical variables. Data are presented as mean ± standard deviation for variables with normal distributions, median (interquartile range) for variables with non normal distributions. Statistical significance level was taken as p <0,05 for all analyzes.

Results

Our study group consisted of 50 (13 girls, 37 boys) children and adolescents with ADHD and 25 (11 girls, 14 boys) healthy children and adolescents. The mean age of the ADHD group was 9.16 ± 1.74 and the mean age of the control group was 9.88 ± 1.53. There was no significant difference between the groups when both groups were compared in terms of mean age (Z= 1.831,p = 0.067) and gender (x^2=2.482, p = 0.115).

Comorbid conditions for ADHD included conduct disorder (18%), oppositional defiant disorder (30%), enuresis (8%) and encopresis (2%).

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It was determined that 70% (n = 35) was combined presentation of ADHD and 30% (n = 15) was attention deficit presentation of ADHD.

ADHD subgroups was evaluated in terms of Parental Conners scores, the mean scores of patients with ADHD attention deficit presentation were 48.20 ± 21.17 and the mean scores of patients with ADHD combined presentation were 49.86 ± 19.31 (Table 1).

ADHD group was assessed in terms of Teachers' Conners form scores, ADHD was 41.49 ± 13.45 points in combined presentation and ADHD was 29.67 ± 6.09 in presentation of attention deficit (Table 1).

The mean plasma suPAR levels of ADHD patients were 2.92 ± 1.74 ng/ml, the controls suPAR levels were 2.54 ± 1.05 ng/ml and there was no significant difference between ADHD and the controls (Z=0.084, p=0.933) suPAR levels (Table 2). No correlation was found between plasma suPAR levels and ADHD severity which assessed by Conner's parent and teacher scales (p>0.05).

SuPAR levels evaluated in terms of ADHD presentations, it was 2.75 ± 1.58 for combined presentation and it was 3.34 ± 2.06 for attention deficit presentation. There was no statistically significant difference between the two presentation of ADHD in terms of suPAR levels (Z=0.922, p = 0.357) (Table 3).

There was no statistically significant difference in suPAR levels between the control group and combined presentation of ADHD and attention deficit presentation of ADHD (respectively, Z=0.316, p=0.752; Z=0.798, p=0.425).

Discussion

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In our study, although the plasma suPAR level, which is a marker of inflammation and immunological activation, tended to be higher in the ADHD group than controls, the difference was not statistically significant. There were no significant difference between the ADHD subgroups and controls. No correlation was found between plasma suPAR levels and ADHD severity which assessed by Conner's parent and teacher scales.

There is limited study on the neuroinflammatory bases of ADHD (21) whereas there is no study evaluating suPAR level with ADHD. Recent studies have demonstrated that there is a possible relationship between immune processes and inflammatory mediators (e.g. cytokines) in ADHD. The dysregulation of proinflammatory cytokines is suggested to play an important role in the etiopathogenesis of ADHD (22). Oades et al (2010) reported that IL 2, IL 6, IL 10, IL 16 were tend to increase, IL -13 and IFN-γ levels were elevated in children with ADHD group compared to other groups (2). Another study IL -6 and IL -10 levels were higher in ADHD subjects compared to the control group (23). It has been emphasized that PKA, which controls inflammatory responses in the brain, controls the expression of some important cytokines such as IL-6, induces the production of the uPAR (5,7) and has a critical role in brain development. In one study, authors suggested that plasminogen activators, inhibitors and uPAR are integral to the pathogenesis of depression (24). Also, it was reported that the cerebral cortical neurons secrete uPAR during the course of post-hypoxic recovery and uPAR takes role in the regeneration of the central nervous system (25) . Although hypoxia is known to have been implicated in the etiology of ADHD (26), there is no study of the association of ADHD and uPAR.

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Inflammatory stimulant-releasing proteases cause circulating u-PAR release from the cell surface and formation of the soluble form of suPAR. Higher suPAR levels are considered as indicator of the low grade inflammation and has prognostic value in various diseases (27). Inflammatory parameters (such as CRP, IL-6 and procalcitonin) correlate with suPAR levels (28). Among the psychiatric disorders, suPAR has only been studied in schizophrenia and bipolar disorder (BD) . Assesing the studies evaluating the relationship between psychiatric disorders and suPAR, suPAR levels were significantly higher than healthy controls in a study investigating the role of inflammation in the etiology of schizophrenia (12) . In another study, plasma suPAR levels of male patients with schizophrenia who were in acute state were evaluated and compared with healthy controls but there was no significant difference (11) . Serum suPAR levels are found to be lower in BD patients with acute periods than in patients with euthymic episodes and healthy controls (29). In addition, it was found that individuals with high suPAR levels were more likely to attempt to commit suicide (13).

Although a possible role of inflammation in the etiology of ADHD is shown in studies performed, we found no significant relation between ADHD and suPAR levels. More studies are needed with suPAR in pathophysiology of psychiatric disorders and in which should be evaluated in more detail in relation to ADHD..

Limitations

Further longitudinal studies with larger sample size might be more explanatory in understanding the role of suPAR in the pathophysiology of ADHD. Also, white blood cell (WBC) count, CRP and suPAR levels were not correlated in our study. And unevaluated

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factors such as history of alcohol abuse and liver disease, high body mass index, unhealthy diet and low high density lipoprotein levels should be evaluated with suPAR levels.

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REFERENCES

1. Thapar A, Cooper M, Eyre O, Langley K. Practitioner review: what have we learnt about the causes of ADHD? Journal of Child Psychology and Psychiatry 2013; 54(1):3-16.

2. Oades RD, Myint A-M, Dauvermann MR, Schimmelmann BG, Schwarz MJ. Attention-deficit hyperactivity disorder (ADHD) and glial integrity: an exploration of associations of cytokines and kynurenine metabolites with symptoms and attention. Behavioral and Brain Functions 2010; 6(1):32.

3. Schmitt J, Chen CM, Apfelbacher C, Lehmann I, Herbarth O, Schaaf B et al. Infant eczema, infant sleeping problems, and mental health at 10 years of age: the prospective birth cohort study LISAplus. Allergy 2011;66(3):404-11.

4. Mitchell RH, Goldstein BI. Inflammation in children and adolescents with neuropsychiatric disorders: a systematic review. Journal of the American Academy of Child & Adolescent Psychiatry 2014; 53(3):274-96.

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5. Donev R, Thome J. Inflammation: good or bad for ADHD? ADHD Attention Deficit and Hyperactivity Disorders 2010; 2(4):257-66.

6. Anisman H, Kokkinidis L, Merali Z. Interleukin-2 decreases accumbal dopamine efflux and responding for rewarding lateral hypothalamic stimulation. Brain Research 1996; 731(1-2):1-11.

7. Tran H, Maurer F, Nagamine Y. Stabilization of urokinase and urokinase receptor mRNAs by HuR is linked to its cytoplasmic accumulation induced by activated mitogen-activated protein kinase-activated protein kinase 2. Molecular and Cellular Biology 2003; 23(20):7177-88.

8. Atkins CM, Oliva Jr AA, Alonso OF, Pearse DD, Bramlett HM, Dietrich WD. Modulation of the cAMP signaling pathway after traumatic brain injury. Experimental Neurology 2007; 208(1):145-58.

9. Fredriksson A, Archer T. Neurobehavioural deficits associated with apoptotic neurodegeneration and vulnerability for ADHD. Neurotoxicity Research 2004; 6(6):435-56.

10. Thun M, Macho B, Eugen-Olsen J. suPAR: the molecular crystal ball. Disease Markers. 2009; 27(3-4):157-72.

11. Genc A, Kalelioglu T, Karamustafalioglu N, Tasdemir A, Genc ES, Akkus M et al. Serum soluble urokinase-type plasminogen activator receptor levels in male patients with acute exacerbation of schizophrenia. Psychiatry Research 2016; 236:179-81.

12. Nielsen J, Roge R, Pristed SG, Viuff AG, Ullum H, Thorner LW et al. Soluble urokinase-type plasminogen activator receptor levels in patients with schizophrenia. Schizophrenia Bulletin 2014; 41(3):764-71.

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13. Ventorp F, Gustafsson A, Träskman-Bendz L, Westrin Å, Ljunggren L. Increased soluble urokinase-type plasminogen activator receptor (suPAR) levels in plasma of suicide attempters. PloS One 2015; 10(10):e0140052.

14. Gökler B, Ünal F, Pehlivantürk B, Kültür EÇ, Akdemir D, Taner Y. Reliability and Validity of Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version-Turkish Version (K-SADS-PL-T). Turkish Journal of Child and Adolescent Mental Health 2004; 11(3):109-16.

15. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P et al. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. Journal of the American Academy of Child & Adolescent Psychiatry 1997; 36(7):980-8.

16. Kaner S, Buyukuzturk S, Iseri E. Conners teacher rating scale-revised short: Turkish adaptation study. Education and Science 2013;38(167):81-97.

17. Kaner S, Buyukozturk S, Iseri E. Conners parent rating scale-revised short: Turkish standardization study/Conners anababa dereceleme olcegi-yenilenmis kisa: Turkiye stardardizasyon calismasi. Archives of Neuropsychiatry 2013; 50(2):100-10.

18. Conners CK, Sitarenios G, Parker JD, Epstein JN. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. Journal of Abnormal Child Psychology 1998; 26(4):257-68.

19. Conners CK, Sitarenios G, Parker JD, Epstein JN. Revision and restandardization of the Conners Teacher Rating Scale (CTRS-R): factor structure, reliability, and criterion validity. Journal of Abnormal Child Psychology 1998; 26(4):279-91.

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20. Dereboy Ç, Şenol S, Şener Ş, Dereboy F. Conners Kısa Form Öğretmen ve Ana Baba Derecelendirme Ölçeklerinin Geçerliği. Türk Psikiyatri Dergisi 2007; 18(1):48-58.

21. Williams K. Autoimmunity as a Risk Factor for Attention-Deficit/Hyperactivity Disorder Journal of the American Academy of Child & Adolescent Psychiatry 2017; 56(3):185-6.

22. Chen M-H, Su T-P, Chen Y-S, Hsu J-W, Huang K-L, Chang W-H et al. Comorbidity of allergic and autoimmune diseases among patients with ADHD: a nationwide population-based study. Journal of Attention Disorders 2017; 21(3):219-27.

23. Donfrancesco R, Nativio P, Di Benedetto A, Villa MP, Andriola E, Melegari MG et al. Anti-Yo antibodies in children with ADHD: first results about serum cytokines. Journal of Attention Disorders 2016; https://doi.org/ 10.1177/1087054716643387.

24. Idell R, Florova G, Komissarov A, Shetty S, Girard R, Idell S. The fibrinolytic system: A new target for treatment of depression with psychedelics. Medical Hypotheses 2017; 100:46-53.

25. Yoon SY, Lee YJ, Seo JH, Sung HJ, Park KH, Choi IK et al. uPAR expression under hypoxic conditions depends on iNOS modulated ERK phosphorylation in the MDA-MB-231 breast carcinoma cell line. Cell Research 2006; 16(1):75.

26. Smith TF, Schmidt-Kastner R, McGeary JE, Kaczorowski JA, Knopik VS. Pre- and Perinatal Ischemia-Hypoxia, the Ischemia-Hypoxia Response Pathway, and ADHD Risk. Behavior Genetics 2016; 46(3):467-77.

27. Bilgili B, Cinel İ. The significance of soluble urokinase plasminogen activator receptor (suPAR) in ICU patients. Translational Research 2013; 162(5): 287-96.

UNCORRECTED

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28. Donadello K, Scolletta S, Covajes C, Vincent J- L. suPAR as a prognostic biomarker in sepsis. BMC Medicine 2012; 10(1):2.

29. Ozpercin PU, Kendirlioglu BK, Sozen S, Yüksel O, Cihnioglu R, Kalelioglu T et al. Decreased circulating urokinase plasminogen activator receptor (uPAR) concentration in acute episodes of bipolar disorder; could it be a reflection of axonal injury? . Psychoneuroendocrinology 2018; 90:122-6.

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Table-1. Conners scores of ADHD presentations

	ADHD Presentation	Mean±SD
Conners Parents Form	ADHD-Attention Deficit (n=15)	48.20 ± 21.17
	ADHD-Combined (n=35)	49.86 ± 19.31
Conners Teacher Form	ADHD-Attention Deficit (n=15)	29.67 ± 6.09
	ADHD-Combined (n=35)	41.49 ± 13.45

Table-2. Comparison of groups in terms of suPAR levels

	ADHD (n=50) Median(1st-3rd quartiles)	**Control** (n=25) Median (1st-3rd quartiles)	**Comparison**
suPAR Levels (ng/ml)	2.30 (1.98)	2.20 (0.75)	Z=0.084 p=0.933

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Table-3. Comparison of presentations of ADHD with control group in terms of suPAR levels

	ADHD-Combined (n=35) Median(1st-3rd quartiles)	**ADHD-Attention Deficit** (n=15) Median (1st-3rd quartiles)	**Comparison**
suPAR Levels (ng/ml)	2,20(1,70)	2,70(2,60)	Z=0.92 p = 0.357

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