Comparison of Toxoplasma gondii IgG Antibody Levels in Children and Adolescents with Obsessive-Compulsive Disorder and Attention-Deficit Hyperactivity Disorder with Healthy Controls: A Cross-Sectional Study

Obsesif Kompulsif Bozukluk ve Dikkat Eksikliği Hiperaktivite Bozukluğu Olan Çocuk ve Ergenlerde Toxoplasma Gondii IgG Antikor Düzeylerinin Sağlıklı Kontrollerle Karşılaştırılması: Kesitsel Bir Çalışma

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ABSTRACT

Objective: Obsessive-compulsive disorder (OCD) and Attention-deficit hyperactivity disorder (ADHD) are frequently seen disorders during childhood. One of the etiological factors for both disorders is infectious diseases and T. gondii is one of them. This study was aimed to examine if there is a relation between IgG levels of T. gondii and OCD or ADHD symptoms.

Material and Methods: Of 42 children with OCD, 31 with ADHD and 28 healthy control were included. Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), Moudsley Obession-Compulsion Inventory (MOCI), Child Depression Inventory (CDI), and Screen of Children for anxiety related disorders (SCARED), The Turgay DSM-IV-Based Child and Adolescent Behavioral Disorders Screening and Rating Scale (T-DSM-IV-S) and The Conners' Parent Rating Scale-48 (CPRS-48) were applied. Toxo gondii IgG values ≥3.0 IU/mL were considered to be reactive. SPSS 17.0 was used for analysis. $p<0.050$ was accepted as significant.

Results: The mean age was 12.13 years. Of 56.40% (n=57) were boys. Depression and anxiety symptoms were similar in OCD and controls, but were significantly lower in ADHD. All children with OCD had negative (100%) for IgG levels of T. gondii, whereas 78.60% of controls and 90.30% of children with ADHD had negative for IgG levels of T. gondii. Toxo IgG seropositivity of the control was significantly higher than that of the OCD.

Toxo IgG levels were positively correlated with Turgay's ADHD-Conduct disorder subscale scores in ADHD group ($r=0.650$, $p<0.001$). In the OCD and the control group, there was no correlation between IgG levels and scale scores (for all variables, $p>0.050$).

Conclusion: This study did not verify a relationship between the seropositivity of T. gondii with OCD and ADHD. Further studies are needed with longitudinal follow-up and extended series of patients.

Key Words: ADHD, Children, Toxoplasma gondii, OCD

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ÖZ

Amaç: Obsesif kompulsif bozukluk (OKB) ve Dikkat eksikliği hiperaktivite bozukluğu (DEHB) çocukluk çağında sık görülen bozukluklardır. Her iki bozukluğun da etiyolojik faktörlerinden biri bulaşıcı hastalıklardır ve T. gondii de bunlardan biridir. Bu çalışma, T. gondii'nin IgG düzeyleri ile OKB veya DEHB belirtileri arasında bir ilişki olup olmadığını incelemek amacıyla yapılmıştır.

Gereç ve Yöntemler: Çalışmaya OKB'si olan 42 çocuk, DEHB'si olan 31 çocuk ile 28 sağlıklı kontrol dahil edildi. Çocuklar için Yale-Brown Obsesif-Kompulsif Ölçeği (YB-OKB), Moudsley Obsesyon-Kompulsiyon Envanteri (MOCI), Çocuk Depresyon Ölçeği (CDI) ve Çocuklarda Anksiyete İlişkili Bozuklukları Tarama Ölçeği (ÇATÖ), Turgay DSM-IV Tabanlı Çocuk Ergen Davranış Bozuklukları Tarama ve Derecelendirme Ölçeği (T-DSM-IV-S) ve Conners Ebeveyn Değerlendirme Ölçeği-48 (CPRS-48) uygulandı. Toxo gondii IgG değerleri ≥3.0 IU/mL reaktif kabul edildi. Analiz için SPSS 17.0 kullanıldı. $p<0.050$ anlamlı kabul edildi.

Bulgular: Ortalama yaş 12,13 yıl ve olguların %56.40'ı (n = 57) erkekti. Depresyon ve anksiyete belirtileri OKB ve kontrollerde benzerdi, ancak DEHB'de anlamlı derecede düşüktü. OKB'si olan tüm çocukların T. gondii'nin IgG seviyeleri negatifken (%100), kontrollerin %78.60'ı ve DEHB'si olan çocukların %90.30'u T. gondii'nin IgG seviyeleri için negatifti. Kontrolün Toxo IgG seropozitifliği, OKB'ninkinden anlamlı derecede yüksekti. DEHB grubunda Toxo IgG düzeyleri ile Turgay DEHB-Davranış Bozukluğu alt ölçek puanları arasında pozitif korelasyon bulundu ($r=0.650$, $p<0.001$). OKB ve kontrol gruplarında IgG düzeyleri ile CDI, SCARED, DEHB ölçekleri arasında korelasyon saptanmadı (tüm değişkenler için $p>0.050$).

Sonuç: Bu çalışma T. gondii'nin seropozitifliği ile OKB ve DEHB arasındaki ilişkiyi doğrulamamıştır. Uzunlamasına takip ve genişletilmiş hasta serileri ile daha ileri çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: DEHB, Çocuk, Toxoplasma gondii, OKB

INTRODUCTION

Toxoplasma gondii infects about 25-30% of the world population, only a very small proportion of them cause clear clinical findings. This infectious agent causes latent infection in many organs in the body, including the brain. Asymptomatic toxoplasma infection is not considered to be any harm before; but a lot of studies show that toxoplasma-infected patients have higher incidences of especially neuropsychiatric disorders (1,2). Schizophrenia is the most strongly proven disease associated with toxoplasma infection among neuropsychiatric disorders (3-5).

Obsessive-compulsive disorder (OCD) is a common disorder designated by uncontrollable thoughts and compulsive behaviors which cause considerable deterioration in the childs academic, social and family functioning. OCD prevelance in childhood is 1-3% and the majority of cases are symptomatic (6). Etiology of OCD has not been fully understood. It is well-known that obsessive-compulsive disorder (OCD) is influenced by genetic factors that account for about 45-65% of the variance in OCD symptoms in young people (7). There are also environmental risk factors in the etiology of OCD. Some studies have shown that there is association OCD with infectious illness. Not only streptococcocal infection thats results Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) or Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) but also other infectious pathogens may be involved OCD etiology. Toxoplasma gondii infection may play a role in the etyopathogenesis of OCD (8,9). Toxoplasma defined as a neurotropic agent, may conduce directly by affecting cognitive function and neurotransmitter activity. Neuroimmune reaction has also been recommended another etiological cause of OCD. Antibodies of toxoplasma affecting neurons in globus pallidus, caudate and putamen with in basal ganglions indicates local immune reactions. Increased brain levels of dopamine by causing a disturbance in serotonin concentration is to play an important etiologic mechanism not only schizophrenia but also OCD (10).

Attention-deficit hyperactivity disorder (ADHD) is common disorder characterized by a inattention and/or hyperactivity-impulsivity symptomps that impairs academic performance, quality of life and interpersonal relationships. The worldwide pooled prevalence was found to be roughly 5% (11). Although genetic factors have priority in the etiology of ADHD, which is a neurodevelopmental disorder, it may play a role in many environmental factors (12,13). The study about relationship of ADHD and infectious agents are scarce (14). Evidence suggests that dysregulation of dopamine and norepinephrine, are involved in the pathophysiology of ADHD. Toxoplasma genome affects genes for rate-limiting enzymes of dopamine synthesis may play a role ADHD (15). Another explanation is that toxoplasma infection becomes latent neurons and glial cell. Higher levels of cysts were reported in some brain area that are known to contain dopamine that results altered dopamine could have negatory consequences for some brain functions. Limited number of studies investigating the relationship between toxoplasma infection and ADHD resulting in the toxoplasmosis seropositivity has not significant difference between ADHD and control group (16,17). A recent meta-analysis conducted by Nayeri et al. (18) also showed that there was not a significant association between the T. Gondii IgG Ab levels and an increased risk of ADHD. Another study showed that in ADHD subjects with toxoplasma gondii IgG positivity had higher levels of severe ADHD compared to the toxoplasma gondii IgG negative children with ADHD (19). Our hypothesis is that the clinical features of ADHD, rather than an etiological relationship between ADHD and toxoplasma seropositivity, might pose a risk for toxoplasma infection. It is thought that symptoms of ADHD, such as hyperactivity and impulsivity, may predispose a risk for this infection.

OCD and ADHD are both mostly seen neuropsychiatric disturbances in pediatric populations. There is a neurobiological link between OCD and ADHD in terms of neurochemical circuitry, neuropsychological and neuroimaging findings to examine etiological factors underlying the disorders (20). There is, however, there was no study in the literature examining the both disorder at the same time to compare in terms of toxoplasmosis gondii seropositivity. In this study, we aimed to investigate association between Toxoplasma gondii IgG antibody levels in both OCD and ADHD in children and adolescents. Our hypotheses are the following; 1) Toxoplasma gondii seropositivity is higher in OCD and ADHD grup than that of the controls. 2) The OCD and the ADHD samples' seropositivities are comparable.

MATERIAL and METHODS

Patients were recruited from the Outpatient Clinic for Ankara Training and Research Hospital, Department of Child and Adolescent Psychiatry. The following exclusion criteria were applied: Presence of psychiatric disorders such as mental retardation, autism spectrum disorder, schizophrenia, bipolar disorder, major depression, major physical (such as diabetes mellitus, cancer) or neurological (neurodegenerative) diseases, such as epilepsy and using corticosteroids or drugs that affect the immune system in the last 6 months. In this terms, among 52 subjects with OCD, 10 children were excluded because of the 7 of them had major depressive disorder and another 3 had mental retardation. During study time-span, 94 children had ADHD. Among them, 36 of subjects had oppositional defiant disorder, 14 had specific learning disorders, 12 had anxiety disorders, 8 had major depressive disorder and 3 had mental retardation. These subjects were excluded from the study due to the comorbidities they had.

The control group was drawn from of healthy volunteers that were applied for General Pediatric Clinics of Ankara Training and Research Hospital for rutine health examination. Inclusion criteria was that having no any medical problem and normal intelligence level. Healthy subjects who agreed to participate in this study were evaluated by the same hospital's child psychiatrists to carry out their psychiatric examination. The study was approved by Ankara Child Health and Diseases Hematology Oncology SUAM, Clinical Research Ethics Committee (11.06.1018-2018-062).

Psychological assessment and tools used

Clinical and sociodemographic data was recorded in a form prepared by the researchers. OCD and ADHD diagnoses were made according to the DSM-5 criteria by child and adolescent psychiatrist.

Children's Yale–Brown Obsessive–Compulsive Scale (CY-BOCS): The severity of the OCD was assigned using the CY-BOCS, which is a semistructured interview applied by the clinician (21). This scale has a 10-item administered by the clinician to assess OCD obsessions (scores ranging from 0 to 20), compulsions (scores ranging from 0 to 20), and total (scores ranging from 0 to 40) symptom severity in children. Higher total and subscale scores indicate greater or more severe obsessions and/or compulsions.

Maudsley Obsessive Compulsive Questionnaire (MOCI): The OCD symptoms' severity was also assessed by the MOCI, which was a self-reported questionnaire. This tool consists of 30 items involving the obsessional-compulsive complaints with a dichotomous rated as "Yes" which is scored 1 point and "No" answers 0 point. Its Turkish version, which is conducted by Erol et al. (22) was used in this study.

Child Depression Inventory (CDI): This is a 27-item self-report scale that can be applied to children between ages 6-17. Its Turkish validity and reliability study was carried out by Oy (23). The test-retest reliability of the scale was 0.80, and the Cronbach alpha internal consistency coefficient was 0.77. The cut-off point of the scale is 19.

Screen for Child Anxiety and Related Disorders (SCARED): This scale consists of 41 items evaluating the child's anxiety. With a self-report design, each item is given 0, 1 or 2 points, depending on the severity of the symptom. Cut-off point of the total score suggested is 25 points and is thought to indicate the presence of an anxiety disorder. Its Turkish validation study was carried out by Çakmakçı (24). The scales's Cronbach's alpha reliability values for the general scale and subscales ranged from .88 to .91 (24).

The Turgay DSM-IV-Based Child and Adolescent Behavioral Disorders Screening and Rating Scale (T-DSM-IV-S): The T-DSM-IV-S scale was developed by Turgay (25) and consists of 42 items that measure attention-deficit, hyperactivity, impulsivity, and disruptive behaviors. In the present study a shorter version of the scale was used that included 9 attention-deficit items, 6 hyperactivity items, and 3 impulsivity items (25). Parents of children filled out this scale to evaluate the severity of the child's ADHD symptoms as well as to determine concomitant disruptive behavior disorders.

Conners' Parent Rating Scale-48 (CPRS-48): This scale is a 48-item Likert-type scale used to assess problematic behaviors in children. In addition to a total score, there are 5 subscale scores as the following; Conduct problems, impulsivity and hyperactivity, learning problems, anxiety and psychosomatic problems. Dereboy et al. (26) studied this scale's Turkish validity. Similar with T-DSM-IV-S scale, parents of children filled out this scale to evaluate the child's ADHD symptoms as well as other problems as aforementioned.

Sample collection/Serological analysis:

Blood samples were collected from the pediatric patients and healthy children. Separated sera stored at +4°C and analysed within 24 hours. Quantitative determination of IgG antibodies to

T. gondii in patients' was performed using the Architect Toxo IgG assay; which is an automated chemiluminescent microparticle immunoassay, in accordance with the manufacturer's instructions (Abbott, ABD). Samples with concentration values ≥3.0 IU/mL were considered reactive for IgG antibodies to T. gondii, concentration values from 1.60 to 2.90 IU/mL were considered gray zone, and concentration values <1.6 IU/mL were considered nonreactive.

Statistical Analyses

Statistical analyses were performed by SPSS 17 Statistical Analysis program (Chicago Inc., 2008). Continuous variables were expressed as mean and standart deviation and categorical variables as frequency (n) and percentage (%). The OCD, the ADHD and the control groups' continuous variables were compared via ANOVA and Kruskal Wallis tests and categorical ones were analyzed by Fisher's exact and Pearson χ2 tests. Spearman correlation test was used to analyse should there was a relation between the IgG levels and CDI, SCARED and ADHD total scores of the groups. p<0.017 was considered significant in triple comparisons and p<0.050 was considered significant in dual comparisons.

RESULTS

The study consisted of 42 OCD, 31 ADHD and 28 healthy controls. The mean age was 12.13 years (SD=3.37, range 6-17 years). Mean age of the ADHD group was smaller than the other two groups (F(2) = 13.01, p <0.001). Of 56.40% (n = 57) of the cases were boys and 43.60% (n=44) were girls. Male gender was found to be significantly higher in the ADHD group (83.90% vs. 40.50% and 50.0%, respectively, when compared with male rates in the OCD and the control groups; $\chi^2(2)=14.313$, p=0.001). The rate of the patients with ADHD (87.10%) in primary education was significantly higher than the other two groups ($\chi^2(2)=10.094$, p=0.006). Three groups were similar in terms of family structure, number of siblings and socioeconomic level (Table I).

In OCD group (n = 42), 88.1% (n=37) of the children had "contamination" obsessions and 95.2% (n=40) of them had "cleaning-washing" compulsions. As regards the symptoms evaluation, depression and anxiety symptoms examined by the CDI and the SCARED were similar in the OCD and the control groups, but were significantly lower in the ADHD group compared to these two groups. The mean CDI scale score was significantly lower in the ADHD group than in the OCD and control group (F(2) = 138.27, p <0.001). Similar with this, the mean SCARED score was significantly lower in the ADHD group compared to the OCD and the healthy subjects (F(2) = 52.721, p <0.001). Conners 'and Turgay scale scores were naturally higher in the ADHD group compared to the control group (see Table II).

The serology findings revealed that all children with OCD had negative (100%) for T. Gondi IgG, whereas 78.6% of controls and 90.3% of children with ADHD had negative for IgG Ab. While the distribution of Toxoplasma gondii IgG seropositivity rates were similar between the control and the ADHD group (p=0.117), and between the OCD and the ADHD group (p =0.072), T. gondii IgG seropositivity of the control group was found to be significantly higher than the OCD group (p = 0.003) (Table II).

Risk factors for toxoplasma gondii infection such as contact with the cat, eating vegetables and fruits without being washed, contacting the soil, drinking water of unknown origin, undercooked meats consumption were also examined. In our study, these variables that posed a risk for toxoplasma infection were questioned in OCD, ADHD and control groups. They showed similar distribution among the three groups (see Table II).

Table I: Sociodemographic and clinical features of the participants

	Total n = 101	OCD n = 42	ADHD n = 31	Control n = 28	Statistics t, z, F or χ^2	p
Age (year)*	12.13 (3.37)	13.0 (3.26)	9.83 (2.91)	13.39 (2.79)	13.010	0.000
Gender †					14.313	0.001
Girls	44 (43.60)	25 (59.50)	5 (16.10)	14 (50.0)		
Boys	57 (56.40)	17 (40.50)	26 (83.90)	14 (50.0)		
Education†					10.094	0.006
Elemantary	65 (64.40)	23 (54.80)	27 (87.10)	15 (53.60)		
High	36 (35.60)	19 (45.20)	4 (12.90)	13 (46.40)		
Family†					6.270‡	0.129
Nuclear	86 (85.10)	32 (76.20)	28 (90.30)	26 (92.90)		
Large	11 (10.90)	8 (19.0)	1 (3.20)	2 (7.10)		
Single parent	4 (4.0)	2 (4.80)	2 (6.50)	0		
SES†					2.369‡	0.692
Low	26 (25.70)	12 (28.60)	7 (22.60)	7 (25.0)		
Moderate	68 (67.30)	28 (66.70)	20 (64.50)	20 (71.40)		
High	7 (6.90)	2 (4.80)	4 (12.90)	1 (3.60)		

:** *Mean (Standard deviation),* **†:** *n (%),* **‡** *Fisher's exact test* ***n: *Frequency,* ***SES:*** *Socioeconomic status*

Table II: Comparison of the distribution of applied scale scores between the three groups

	OCD n = 42	ADHD n = 31	Control n = 28	Statistics t, F or χ^2	p
Scales*					
CDI	25.09 (3.72)	1.35 (5.34)	21.85 (9.57)	138.27	0.000
SCARED	34.14 (16.55)	1.74 (6.76)	22.28 (13.41)	52.721	0.000
MOCI	49.78 (13.30)	NA	NA	NA	NA
CY-BOCS-Total	21.13 (6.91)	NA	NA	NA	NA
Obsession score	10.54 (3.80)	NA	NA	NA	NA
Compulsion score	10.64 (3.51)	NA	NA	NA	NA
CPRS-48					
CP	NA	16.19 (5.80)	12.42 (4.52)	2.757	0.008
I-HA	NA	10.96 (4.34)	8.03 (3.38)	2.869	0.006
LP	NA	13.83 (4.71)	9.71 (2.92)	3.981	0.000
OB	NA	7.96 (2.56)	5.71 (1.78)	3.881	0.000
Anxiety	NA	16.30 (5.15)	13.89 (4.13)	1.954	0.056
Psychosomatic	NA	8.41 (3.44)	8.64 (3.37)	-.251	0.803
T-DSM-IV-S*					
ADHD-Total	NA	34.0 (10.53)	13.42 (9.41)	7.872	0.000
IA	NA	16.51 (6.19)	7.21 (5.15)	6.232	0.000
HA	NA	17.48 (5.34)	6.21 (5.33)	8.092	0.000
ODD	NA	12.64 (4.72)	6.96 (5.31)	4.347	0.000
CD	NA	5.93 (6.53)	1.82 (2.49)	3.131	0.003
Laboratory					
Toxo-IgG‡				12.018†	0.001
Positive	0	3 (9.70)	2 (7.10)	ADHD vs. Control	0.117
Gray zone	0	0	4 (14.30)	ADHD vs. OCD	0.072
Negative	42 (100.0)	28 (90.30)	22 (78.60)	OCD vs. Control	0.003
T. gondii related factors					
Residency‡				11.841†	0.009§
City	30 (71.40)	25 (80.60)	81 (80.20)		
Rural area	1 (2.40)	3 (9.70)	2 (7.10)		
NA	11 (26.20)	3 (9.70)	0		
Contact with cat‡				15.218†	0.003§
Yes	4 (9.50)	9 (29.0)	3 (10.70)		
No	27 (64.30)	19 (61.30)	25 (89.30)		
NA	11 (26.20)	3 (9.70)	0		
Eating raw meat‡				14.306†	0.005§
Yes	8 (19.0)	6 (19.40)	2 (7.10)		
No	23 (54.80)	22 (71.0)	26 (92.90)		
NA	11 (26.20)	3 (9.7)	0		
Soil contact‡				13.125†	0.006§
Yes	26 (61.90)	27 (87.10)	26 (92.90)		
No	5 (11.90)	1 (3.20)	2 (7.10)		
NA	11 (26.20)	3 (9.70)	0		
Eating vegetable without washing‡				13.988†	0.006§
Yes	16 (38.10)	16 (51.60)	11 (39.30)		
No	14 (33.30)	12 (38.70)	17 (60.70)		
NA	12 (28.60)	3 (9.70)	0		
Drinking water of unknown origin‡				10.354†	0.031§
Yes	20 (48.80)	21 (67.70)	18 (64.30)		
No	11 (26.80)	7 (22.60)	10 (35.70)		
NA	10 (24.40)	3 (9.70)	0		

:** *Mean (standard deviation),* **†:** *Fisher's exact test,* **‡:** *n (%),* **§:** *Not-significant after controlling NA,* ***CDI: *Child depression inventory,* ***SCARED:*** *Screen for childhood anxiety related disorders,* ***MOCI:*** *Maudsley Obsessive-Compulsive,* ***CY-BOCS:*** *Children's Yale-Brown Obsessive-Compulsive Scale,* ***CPRS-48:*** *Conners' Parent Rating Scale-48,* ***T-DSM-IV-S :*** *Turgay DSM-IV-Based Child and Adolescent Behavioral Disorders Screening and Rating Scale,* ***CP:*** *Conduct problem,* ***I-HA:*** *Impulsivity-hyperactivity,* ***LP:*** *Learning problem,* ***OB:*** *Oppositional behavior,* ***IA:*** *Inattention,* ***HA:*** *Hyperactivity,* ***ODD:*** *Oppositional defiant disorder,* ***CD:*** *Conduct disorder.* ***NA:*** *not-applicable.*

Table III: Correlation between IgG levels (IU/ml) and CDI, SCARED and ADHD total scores of the groups

	IgG levels (IU/ml)					
	ADHD (n = 31)		OCD (n = 42)		Control (n = 28)	
	Spearman r	p	Spearman r	p	Spearman r	p
CDI	-0.051	0.785	-0.092	0.560	0.009	0.963
SCARED	-0.054	0.775	-0.269	0.085	0.048	0.808
T-DSM-IV-S						
ADHD-Total	-0.093	0.617	NA	-	0.323	0.093
ADHD-IA	-0.061	0.743	NA	-	0.279	0.150
ADHD-HA	-0.113	0.545	NA	-	0.302	0.119
ADHD-ODD	0.039	0.835	NA	-	0.136	0.491
ADHD-CD	0.650	0.000	NA	-	0.157	0.425
CPRS-48						
CPRS-CP	0.083	0.657	NA	-	0.370	0.052
CPRS-I-HA	-0.248	0.179	NA	-	0.000	0.999
CPRS-LP	-0.092	0.621	NA	-	0.289	0.135
CPRS-OB	-0.124	0.507	NA	-	-0.077	0.699
CPRS-Anxiety	-0.242	0.197	NA	-	0.057	0.772
Psychosomatic	-0.152	0.413	NA	-	0.191	0.330
MOCI-Total	NA	-	0.200	0.204	NA	-
CY-BOCS-Total	NA	-	0.154	0.330	NA	-
Obsession	NA	-	0.112	0.481	NA	-
Compulsion	NA	-	0.184	0.242	NA	-
OCD symptoms						
Contamination (n=37)	NA	-	0.010	0.952	NA	-
Cleaning-washing (n = 40)	NA	-	0.135	0.394	NA	-

CDI: *Child depression inventory,* ***SCARED:*** *Screen for childhood anxiety related disorders,* ***T-DSM-IV-S:*** *Turgay's DSM-IV-Based Child and Adolescent Behavioral Disorders Screening and Rating Scale,* ***ADHD-Total:*** *Turgay's ADHD scale-total,* ***HA:*** *Hyperactivity,* ***ODD:*** *Oppositional defiant disorder,* ***CD:*** *Conduct disorder,* ***CPRS-48:*** *Conners' Parent Rating Scale-48,* ***CP:*** *Conduct problem,* ***I-HA:*** *Impulsivity-hyperactivity,* ***LP:*** *Learning problem,* ***OB:*** *Oppositional behavior,* ***MOCI:*** *Maudsley Obsessive-Compulsive,* ***CY-BOCS:*** *Children's Yale-Brown Obsessive-Compulsive Scale,* ***NA:*** *not-applicable,* ***r:*** *Spearman rho correlation coefficient*

The Spearman correlation analysis revealed that in the ADHD group (n = 31), Toxo IgG levels were positively correlated with Turgay's ADHD-Conduct disorder subscale scores (Spearman r = 0.650, p <0.001). In the OCD (n = 42) and the control (n = 28) groups, there was no correlation between IgG levels and the CDI, the SCARED, the ADHD scales (for all variables, p>0.050). In the OCD group, there was also not any correlation found in terms of obsession or compulsion symptom dominancy and IgG levels. Neither the contamination obsessions nor the cleaning-washing compulsions was correlated with T. gondii IgG Ab levels (for both, p>0.050). Interestingly, there was a positive correlation between CPRS-48 conduct problems (CPRS-CP) scores and IgG levels in borderline- terms (Spearman rho = 0.370, p = 0.052) (see Table III).

DISCUSSION

This study aimed to evaluate T. gondii IgG seropositivity in children with OCD and ADHD and to compare with healthy counterparts. Although there was no association between OCD and T. gondii IgG seropositivity, an association between IgG Ab levels and conduct disorder symptoms in children with ADHD was found. This intruiging result is worth further studying, since conduct disorder is an externalizing problem. Supporting this issue, there was found a significant low level of the CDI and the SCARED scores of children with ADHD compared to the OCD and the healthy subjects. It might be ADHD is, as a whole, an externalizing disorder compared to the other internalizing disturbances including the OCD.

Although recent studies have attempted to elucidate the relationship between different type of infectious agents and psychiatric disorders, data are particularly limited in pediatric age group and there are conflicting results (27-29). Among the different type of pathogens associated with psychiatric disorders, the plurality of attention is T. gondii infectious, that has a lifelong asymptomatic latent phase in patients after a short acute period. In the recent meta-analysis and systematic review show that a toxoplasma infection is an associated factor for bipolar, schizophrenia epilepsy, but not for depression (30-33). Few studies have been conducted to investigate the possible relationship between OCD and T. gondii infection both adulthood and childhood. The first studies on this subject in the literature were case reports. Two children with toxoplasmosis and OCD showed significant reduction in the symptoms of OCD with antiprotozoal drugs (34). Similarly, there is one reports of adult case with antiprotozoal medications that show a decrease in OCD symptoms (35). The association between T.

Gondi and OCD is not clearly identified and there are conflicting results in researchs. In some studies, seroposivity rate for T. Gondi infection among OCD are considerably higher than the control group (36,37). On the other hands in many studies, no differences were found between toxoplasma seropositivity between OCD patients and control group (38-40). In a recent meta-analysis, conducted Chegeni et al. (41) which compiled 11 studies on the subject, a quarter of 389 OCD patients and roughly 17% of 9484 controls were positive for toxoplasmosis. This systematic review revealed that toxoplasma infection could be as an associated factor for OCD (OR = 1.96). Different results of investigation appraised the relationship between various variables including sex, age, education and socio-economic level, and place of residence. In our study we asked the patient and the control group should they contact with the cat, eating vegetables and fruits without being washed so forth. Although these variables have been determined according to patients' declaration; the risk factors for toxoplasma infection did not differ in the patient and control groups contributed to the exclusion of confounding factors in our study. Conflicting results in studies may have an impact on changes in specificity and sensitivity ELISA test kits and different cut-off rate are factors that affect the infection prevelance. In our study, T. Gondi Ig G seropositivity was significantly higher in the control group compared to the OCD group in contrast to previous studies. It has been shown that the most common obsessions in children are rituals for contamination and aggression, and the most common compulsions are washing and avoiding harm. Similarly, in our study, 88.1% (n=37) of the patients had contamination obsessions and 95.2% (n=40) of the cleaning-washing compulsions.

In a study, conducted by Shehataa et al. (42) that examined the relationship between neurodevelopmental disorders and toxoplasma, the only related factor was age and seropositivity increased with age. Miman et al. (36) investigated toxoplasma infection in adult OCD patients, toxoplasma was a risk factor for OCD, but the same researcher did not show the same relationship in a later study in children and adolescents (43). Authors stated that this difference in adulthood and childhood may be related to the different nature of adulthood onset and childhood onset OCD in these periods. Even in our study, T. gondii IgG seropositivity of the control group was significantly higher than the OCD group. Considering the symptomatology of OCD, the most common type of contamination obsessions in children may decrease the risk of children becoming infected with toxoplasma. In our study, the presence of either contamination obsessions or cleaning-washing compulsions were not found correlated with T. gondii IgG Ab levels. This is result is might be a result of relatively limited number of OCD subjects.

Although the relationship between many psychiatric diseases and toxoplasma infection has been examined before, a few studies investigating the toxoplasma infection as a risk factor for ADHD (16,17). Toxoplasmosis seropositivity has not significant difference between ADHD and control group in two study as in our study. These two studies included children and adolescents. In another study, conducted by Shehataa et al. (41) seropositivity of anti-Toxoplasma IgG was significantly associated with non-schizophrenic neurodevelopmental disorders including ADHD, autism, speech and language development delay. But this study includes both child-adolescent and adult age groups and it was a statistically significant difference between toxoplasma IgG seropositivity regarding the age of the patients. If the group divided into to be less than 20 and greater than 20, 20 years or older were twice more likely exposed to T. Gondii than those younger than 20 years old. In addition, the number of ADHD cases in this study (n=14) is very low. It was thought that the clinical features of ADHD like impulsivity might pose a risk for toxoplasma infection. But in our study, no relationship was found between toxoplasmosis and any clinical signs of ADHD (attention, hyperactivity, impulsivity). On the other hands, Toxo IgG levels were positively correlated with Turgay's ADHD-Conduct disorder subscale scores. It may be related to the low level of socioeconomic level and less compliance with hygiene rules of the group with conduct disorder. It is thought that larger sample and follow-up studies are needed to demonstrate this causal relationship. Also in the literature, there is no study showing the relationship between toxoplasmosis infection and adulthood ADHD. We suggest that in the future research are need larger amount of individuals and adult age group.

This study's strenght point is to examine T. gondii IgG seropositivity levels in children with ADHD and the OCD and compare with healthy subjects. Including these two mostly seen disturbances in childhood period at the same study is a strength. There is, however, some limitations. First, this was a clinical study and findings could not be generated. Second, although three groups were included, sample numbers were relatively limited.

To conclude, this study did not verify a relationship between the T. gondii and OCD. There is however, findings suggest that there might be an association between IgG Ab levels and depressive or anxiety symptoms in children with ADHD and, even, there may be a relation between hyperactivity symptoms and IgG levels in healthy children. Further studies are needed longitudinal follow-up and extended series of patients.

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