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Research / Araştırma

# The Seroprevalence of Antibodies to Toxoplasma Gondii Among Children with Autism

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**ABSTRACT**

The seroprevalence of antibodies to Toxoplasma gondii among children with autism

**Objective:** Although attempts have been made to explain the pathogenesis of autism spectrum disorders (ASD) with many factors such as genetic, immunological, environmental, and infectious agents, this mechanism remains for the most part unknown. Toxoplasma gondii is a parasite that is investigated in many psychiatric diseases. This work examines whether toxoplasmosis plays a role in the pathogenesis of ASD through a seroprevalence study.

**Method:** This study is based on a comparison of 102 children with ASD and 51 healthy children. In addition to routine laboratory tests, a sociodemographic form and a childhood autism rating scale were completed and the participants' anti-toxoplasma IgM and IgG titers were requested.

**Results:** In 3 ASD children (2.9%) and in 1 control (2%), IgG positivity was identified. All subjects were negative for IgM. There was no statistically significant difference found between the two groups in terms of toxoplasma seropositivity.

**Conclusion:** Our data does not confirm the involvement of toxoplasmosis in the etiopathogenesis of ASD.

**Keywords:** Autism, autism spectrum disorder, toxoplasmosis, Toxoplasma Gondii

**ÖZET**

Otizmli çocuklarda Toxoplasma gondii antikorlarının seroprevalansı

**Amaç:** Otizm spektrum bozukluğu patogenezi genetik, immünolojik, çevresel ve enfeksiyöz ajanlar gibi pek çok nedenle açıklanmaya çalışılmasına rağmen hala büyük oranda nedeni bilinmeyen bir durumdur. Toxoplasma Gondii de çok sayıda psikiyatrik hastalıkta araştırılmış bir parazittir. Bu çalışmada ASD patogenezinde toxoplasmosisin rolü olup olmadığı seroprevelans çalışması ile araştırılmıştır.

**Yöntem:** Yüz iki OSB'li çocuk ve 51 sağlıklı çocuk karşılaştırılmıştır. Rutin labarotuar testlerinin yanında sosyodemografik form ve çocukluk çağı otizm derecelendirme ölçeği uygulanmış ve anti-toksoplazma IgM ve IgG titreleri istenmiştir.

**Bulgular:** Üç OSB'li çocuk (%2.9) ve 1 kontrolde (%2) IgG pozitif bulunmuştur. Bütün deneklerde IgM negatif olarak bulunmuştur. İki grup arasında toxoplazma seropozitivitesi açısından istatistiki olarak anlamalı bir fark bulunamamıştır.

**Sonuç:** Ulaştığımız bu bilgi OSB etyopatogenezinde toxoplazmozisin bir ilgisinin olduğunu desteklememektedir.

**Anahtar kelimeler:** Otizm, otizm spektrum bozukluğu, toksoplazmozis, Toxoplasma Gondii

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## INTRODUCTION

Autism spectrum disorder (ASD) is a disorder defined by incompetence for social interaction and communication and limited and repeated (stereotypic) behavior and interest that begins in the early stages of development (1). In recent epidemiologic studies, its estimated prevalence is about 1% (2,3). Assessed as a multifactorial disorder involving the interaction of neurologic, immunologic, environmental and genetic factors, the cause of autistic disorder is still not fully known (4).

Toxoplasma gondii (T. gondii) is an intracellular parasite affecting up to 30% of the global population (5). T. gondii has a high affinity to brain tissue. T. gondii may cause neuronal damage, affecting the hypothalamic-pituitary-adrenal functions and interacting with certain genes as well as affecting the synthesis of neurotransmitters like dopamine and serotonin (6). Toxoplasmosis has been investigated in the context of many psychiatric diseases such as schizophrenia, bipolar disorder, obsessive compulsive disorder, depression, anxiety disorder, personality changes, suicide, and even traffic accidents (7-18). The effect of a T. gondii infection in the early period of life occurs at the neurodevelopmental stage. Thus, children are particularly a high risk (19). As toxoplasma especially affects the central nervous system (CNS) initially, infection during childhood may cause neurodegeneration, resulting in the insufficient functioning of the CNS. Some authors found a higher rate of toxoplasma antibodies in children and adolescents struggling with education compared to normal children and adolescents of the same age, which supports this hypothesis (20). During its life cycle, T. gondii interacts with up to 3000 host genes and proteins, which may includes genes related to multiple sclerosis, Alzheimer's and Parkinson's Diseases, schizophrenia, bipolar disorder, depression, childhood obesity, attention deficit and hyperactivity disorder, and autism among others (21). It has been indicated that damage to areas of the brain such as the neocortex, limbic cortex and primitive striatal complex found in childhood autism may be caused by a variety of factors linked to toxoplasma (22). One of the effects of toxoplasma is that it causes an increase in dopamine which may affect human behavior and cause psychiatric diseases (23). There is also an increase in dopamine metabolism reported in ASD (25,26). In terms of neuropathological changes and clinical appearance, there are similarities between ASD and congenital and chronic latent toxoplasmosis. These similarities have led to the idea that T. gondii could be a significant infectious factor that may trigger the development of ASD, obsessive compulsive disorder, attention deficit-hyperactivity disorder, and some other neurodegenerative diseases like cryptogenic epilepsy (27). Additionally, latent toxoplasmosis is reactive to the effects of some environmental factors and has been suggested to result in the development of ASD (28). This study tested the hypothesis of a possible correlation between ASD and toxoplasmosis through seroprevalence research.

## METHOD

This case-control study was completed at the Pediatric and Adolescent Psychiatry, Pediatric and Microbiology Departments of Ordu University's Faculty of Medicine, Training and Research Hospital from March 2015-March 2016. The study included 102 ASD patients (aged 3-16.5 years) and 51 healthy controls (aged 3.5-14 years). Children with ASD were recruited from the pediatric and adolescent psychiatry outpatient clinic. This hospital contains the only pediatric and adolescent psychiatric center in the region. Healthy children were recruited from the pediatric clinic and the pediatric psychiatric clinic of Ordu University Hospital with the condition of having either no psychiatric diagnosis or only minor diseases. Patients using antibiotics were excluded from the study due to the possibility of affecting toxoplasma seropositivity. Consent was obtained from the family of each participant. The study received permission from the Ordu University ethics committee.

### Measures

Sociodemographic data included age, sex, residence, pregnancy, and birth history, onset of disease, medical history, family history, duration of breastfeeding, education, and medications used. The Childhood autism rating scale (CARS) consists of 15 items that are used to generate a total score defining the severity of autism. A total score between 30 and 36.5 indicates mild to moderate autism, whereas the interval between 37 and 60 denotes severe autism. CARS is scored by observing the child and through interviews conducted with the family (29).

### Procedure

As a result of detailed clinical observation and family interviews, 102 ASD children were diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders-5 (APA 2013). A general examination was performed for each participant by expert pediatricians. Additionally, all subjects completed the Childhood Autism Rating Scale (CARS) and a sociodemographic form, and routine laboratory and toxoplasma IgM and IgG values were requested.

### Laboratory Assessment

Blood samples were taken from participants between 8 am and 11 am. On the same day, hemogram, routine biochemistry, thyroid function, and toxoplasma IgM and IgG antibodies were studied. Toxoplasma IgM and IgG were studied in patient and control serum using electrochemiluminescence immunoassay (ECLIA-Roche, Elecsys) according to the manufacturer's instructions. Internal and external quality control of the kits was performed and recorded. Results were assessed as positive or negative. While assessing results, in accordance with the trade kit evaluation criteria for ECLIA-Roche, Elecsys Anti-T. gondii IgM values >1.0 S/CO values were positive and for anti-T. gondii IgG ≥3.0 IU/ml were positive.

### Statistical Analysis

All statistical analyses were performed with SPSS 17.0 for Windows software (SPSS Inc., Chicago, IL, USA). According to the G power analysis results, in this study with 80% power and 5% type-1 error, when the expected rate in the control group is accepted as 4%, there must be at least 1861 subjects in each group for a 2% difference to be considered significant. Data are presented as the number of cases and percentage for categorical variables (seroprevalance, gender, etc.), and as the mean with standard deviation for ages and CARS values. The difference between the patient and control groups in terms of ages and CARS values was determined using the Student t-test. Chi-square and Fisher's exact tests were applied to determine whether there was a relationship between IgG (negative and positive), gender, and group membership (control vs. patient). A p-value of <0.05 was considered statistically significant.

## RESULTS

No statistically significant difference was found in terms of the ages between the patient group (7.63±3.46) and the control group (7.47±3.40) (p=0.784). However, a statistically significant difference was found in terms of the CARS values between the patient group

**Table 1: Descriptive statistics of the examined variable (age and CARS) for the groups**

| Parameters | Groups | n | Mean | Std. Deviation | Minimum | Maximum | t | p |
|---|---|---|---|---|---|---|---|---|
| **Ages** | Control | 51 | 7.47 | 3.40 | 3.50 | 14.00 | -0.275 | 0.784 |
| | Patient | 102 | 7.63 | 3.46 | 3.00 | 16.50 | | |
| | Total | 153 | 7.58 | 3.43 | 3.00 | 16.50 | | |
| **CARS** | Control | 51 | 15.00 | 0.00 | 15.00 | 15.00 | -30.585 | <0.001 |
| | Patient | 102 | 47.15 | 7.49 | 30.00 | 60.00 | | |
| | Total | 153 | 36.43 | 16.39 | 15.00 | 60.00 | | |

CARS: Childhood Autism Rating Scale

**Table 2: Frequencies and percentages (n [%]) of the examined variables (Sex and IgG) for the groups**

| Variables | Groups | | | | | |
|---|---|---|---|---|---|---|
| | Control | | Patient | | | |
| | n | % | n | % | $\chi^2$ | p |
| **Sex** | | | | | 2.448 | 0.137 |
| Male | 37 | 72.55 | 85 | 83.33 | | |
| Female | 14 | 27.45 | 17 | 16.66 | | |
| **IgG** | | | | | 0.128 | 0.593 |
| Negative | 50 | 98.00 | 99 | 97.05 | | |
| Positive | 1 | 2.00 | 3 | 2.95 | | |

IgG: Anti-toxoplasma Ig-G; $\chi^2$ value: Chi-square value

(47.15±7.49) and the control group (15.0±0.00) (p<0.001) (Table 1). There was no significant difference between the groups in terms of sex and IgG (p=0.118; p=0.593 respectively) (Table 2).

Of the IgG-positive ASD children, one was a 6.5-year-old male with a CARS score of 47 who used no medication, the second was a 10.5-year-old male with a CARS score of 32.5 who used only 40mg/day atomoxetine, and the third was a 16.5-year-old male with a CARS score of 48 who used multiple antipsychotic medication. In the control group, IgG positivity was observed in a 4-year-old male child with no medical or psychiatric diagnosis or medication use.

## DISCUSSION

This study aimed to present serologic evidence showing the relationship between toxoplasmosis and autism. Serological research was applied to 154 subjects. Toxoplasmosis IgG positivity was 2.9% in the ASD group and 2% in the control group. This result indicates that there was no statistically significant difference between the autistic group and the healthy control group in terms of toxoplasma seropositivity. However, the risk was 1.98 times greater for IgG-positive individuals compared to IgG-negative individuals. Additionally, IgG positivity was identified only in males. Toxoplasma IgM was negative in all subjects. To the best of our knowledge, there are only two studies to date on this matter. The first seroprevalence study showed a correlation between toxoplasma and autism in Iran (30). The study examined 40 autistic children and 40 healthy controls. In the autistic group, all subjects were negative for IgM and IgG and in the control group only one child was positive for IgG. This study reached the same conclusion as our study, hence, it appears that both works are in agreement. The second study was completed by Prondota et al. (31). The results of that study found 23.9% of 46 autistic children to be IgG positive, while 4% of 50 control children were positive. There was a statistically significant difference between the two groups. This result contradicts with our findings. The age of the seropositive group was found to be greater than the seronegative group. Of the toxoplasma-positive children, 73% were male and 27% were female. The results by age and gender were similar to those of our study.

Toxoplasmosis is one of the most common infections globally. Epidemiological studies have estimated that nearly one third of the global population is infected (5). Epidemiologic studies in the US have found 22.5% IgG seropositivity, while the incidence increased with age (32). According to epidemiologic studies published in Turkish journals, the mean toxoplasma seropositivity in Turkey is between 23%-35.5% (33-35). Here, too, seropositivity was found to increase with age. A study on children in Turkey found IgG positivity at a level of 8.4% and IgM positivity of 0.4% (36). Our study found that positivity to lower than the mean for general society; however, the risk grows with increasing age. Apart from one subject (an Iraqi refugee), all subjects were from similar

sociocultural backgrounds and residential areas. One of the reasons for low seropositivity may be that in this region of Turkey pet ownership traditionally is not common and the subjects do not live on farms and have no exposure to livestock. The negative IgM result for all subjects leads to the consideration that primary or reactivated toxoplasmosis does not play a role in autism pathogenesis. IgG positivity was only identified in males. Autism is observed more frequently in males; the male/female ratio is reported to be 4:1 (37). It has been proposed that high testosterone levels may contribute to the etiology of ASD in males with latent toxoplasmosis (38,39).

Another reason for low IgG positivity may be that some of the subjects in the autistic patient group used antipsychotics and valproate. Antipsychotic treatment has been identified to reduce antibody levels in schizophrenic patients (40). Additionally, an in vitro study found that antipsychotic medications and valproate inhibited the replication of toxoplasma (41). In the autism patient group, 48.5% (n=50) used antipsychotics. Additionally, while only 1 patient was taking valproate on its own, 4 were taking antipsychotics with valproate. Another reason that may explain the seronegativity is that all the Ig tests may not be sensitive and specific. As explained in an article by Prandota, reduced activation of lymphocyte B cells secreting immunoglobulin due to T. gondii infection, reduced immunoglobulins or autoimmune excessive immunoglobulin production linked to exhausted immune response to T. gondii may cause more IgG negativity (31).

Among the limitations of our study, there are the low seropositivity results and the small sample size. The small number of participants and the resulting low fraction of T. gondii seropositive individuals observed translate to a reduction in power to detect any underlying associations. Another limitation of this study was that only one child and adolescent psychiatrist diagnosed the patients. Another limitation was the broad age range within the groups.

In conclusion, according to the results of this study, toxoplasmosis appears to play no role in the etiology of autism. An advanced research with a higher numbers of subjects using Western blot as the gold standard method is required in order to obtain more definitive results.

| **Contributions category** | **Authors name** |
|---|---|
| Development of study idea | E.E., Y.C. |
| Methodological design of the study | E.E., E.Y.D., A.E., E.Y.E., A.D. |
| Data acquisition and process | E.E., A.E., E.Y.E., A.D. |
| Data analysis and interpretation | E.E., Y.C., M.K.C., A.E., E.Y.E., A.D. |
| Literature review | E.E., E.Y.D., M.K.C. |
| Manuscript writing | E.E. |
| Manuscript review and revisation | E.E., E.Y.D., A.E., E.Y.E., A.D., Y.C., M.K.C. |

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