Review
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Toxoplasmosis and Neuropsychological Effects

Toksoplazmoz ve Nöropsikolojik Etkileri

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ABSTRACT

Toxoplasma gondii is an intracellular protozoan parasite. Approximately 30% of the global population is infected by *T. gondii*. In chronically infected individuals, the parasite resides in tissue cysts, especially in the brain. There is a growing interest in the role of parasitologic agents in the causation of neuropsychological disorders. In this review, we have explained the interactions between *Toxoplasma* and its host, mechanisms, and consequences on neural and psychological diseases.
Keywords: Neuroscience, *Toxoplasma gondii*, central nervous system, neuropsychology

ÖZ

Toxoplasma gondii, hücre içi bir protozoan parazittir. Dünya nüfusunun yaklaşık %30'u *Toxoplasma gondii* ile enfektedir. Kronik olarak enfekte insanlarda, parazit doku kistleri özellikle beyinde bulunur. Nöropsikolojik bozuklukların nedenselliğinde, parazitolojik ajanların rolüne artan bir ilgi vardır. Bu derlemede; *Toxoplasma* spp. ile konağı arasındaki etkileşimleri, nöral ve psikolojik hastalık üzerine mekanizmaları ve sonuçları açıklanmıştır.
Anahtar Kelimeler: Nörobilim, *Toxoplasma gondii*, santral sinir sistemi, nöropsikoloji

INTRODUCTION

Toxoplasma gondii is an obligate intracellular protozoan parasite and can infect and duplicate in any nucleated vertebrate cell (1). Felidae (cat family) are the definitive host for toxoplasma. Cats disseminate the oocysts to the environment by their feces. These oocytes are very resistant and by mixing in the soil they can contaminate the water and some food such as vegetables. Toxoplasma can infect humans in different ways;

• Eating undercooked or raw meat containing tissue cysts (bradyzoites),
• Consuming unclean food (such as vegetables) or contaminated water (oocysts),
• Organ transplantation or blood transfusion (tachyzoites),
• Vertical transmission (transplacental route from mother to fetus) (tachyzoites).

It is the most common parasite affecting one third of the world population (2). It is asymptomatic in about 90% of cases (3).

Toxoplasma can settle anywhere in the body, but predominantly brain, muscle, ocular involvements are seen. Congenital toxoplasmosis is one important issue concerning toxoplasmosis since vertical transmission may affect the unborn baby and may cause a wide range of problems from intracranial calcifications, hydrocephaly, chorioretinitis, deafness to intrauterine fetal demise (4).

Toxoplasma gondii can be divided into 3 main genotypes as I, II and III (5). These types may be of importance in terms of geographic distribution as well as pathogenicity of *Toxoplasma gondii* (6,7).

Until recent data, chronic latent toxoplasmosis has been viewed as a "benign" condition, however it has been proposed and supported mainly by experimental studies that such condition may have devastating effect on neuropsychological system via various introduced mechanisms (8).

Here, we wish to review the proposed toxoplasma-related neuropsychological disorders with the suggested mechanisms. We do hope that this review would be an inspiration to all to scout this fascinating field of toxoplasma and neuroscience.

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Türkiye PARAZİTOLOJİ Dergisi

How Can *Toxoplasma* Transport Into the Brain?

After entering the human body as in the form of tissue cysts, after passing beyond the stomach, the parasite excyst in the gut, cross the gut epithelium, continuing to increase in number. Once it is in the bloodstream, in its intracellular allocation, it can be transferred all across the body. Toxoplasma has a particular tropism for muscle and brain tissues where it may remain in a cystic form in a human's lifetime.

Fundamentally the brain is protected by 3 major guardians; the arachnoid epithelium, the choroid plexus epithelium and blood brain barrier (BBB) (9). BBB is an important checkpoint for big proteins, large peptides. There are three different mechanisms proposed for the traverse of *Toxoplasma* spp. cross the BBB (10);

1. Paracellular entry: *T. gondii*, by using its gliding ability (actin-myosin), can use tight junction proteins in the endothelial cell layer and slide into neighbouring cells.

2. Transcellular entry: Tachyzoites can invade the endothelial cells, propagate in the cells, and then burst the cells.

3. Stowaway entry ("Trojan horse"): Infected monocytes or dendritic cells can cross BBB and then deliver the parasites in.

The Relationship Between Toxoplasmosis and Neuropsychiatric Diseases

Attention to the relationship between toxoplasmosis and neuropsychiatric diseases was first drawn in 1953, when high prevalence of toxoplasma positivity was found among patients in the psychiatric department (11). Although now the skin test is abandoned due to low sensitivity, this study definitely has historical importance. Here, we present the diseases on which the link with toxoplasmosis was studied in the literature.

Alzheimer's Disease

Alzheimer's disease (AD) is the most common neurodegenerative disease in the world (12). It is marked with cognitive and behavioural impairment. Although it has been described by Alois Alzheimer back in 1907, it is still a disease yet to be fully understood (13). There are two main characteristics of the disease: the abnormal configuration and excessive phosphorylation of amyloid deposition and neurofibrillary tangles in neurons.

Since toxoplasmosis affects cognition and behaviors, studies investigated if there was any link between toxoplasmosis and AD. In one experimental study, beta-amyloid plaque deposition was found to be less in infected mice compared with an uninfected control group (14). Again, in another experimental study, clearance of beta-amyloid plaque has been shown in the murine model of AD (15). This finding was attributed to inflammation-induced beta-amyloid phagocytosis and degradation.

Seropositivity for *T. gondii* antibodies was almost doubled in patients with AD when compared with the control groups (42.3 vs 22.5%, respectively) (16). More recent case-control study, however, did not show higher prevalence of toxoplasma antibodies in patients with AD (17). In 2019, there have been 2 systematic reviews and meta-analyses by two different groups of investigators; one suggested that *T. gondii* can be considered as a risk factor for developing AD [odd ratio (OR): 1.53, 95% confidence interval (CI): 1.07-2.08, and the other found marginally significant (OR: 1.38, 95% CI: 0.99-1.92] associative link between toxoplasmosis and AD.

The diversity between the experimental and clinical studies is difficult to explain. It may be due to several factors. First, it is not always possible to extrapolate the experimental studies to humans. Secondly, pathophysiology is not crystal clear for AD, as in many neurological diseases, and there may be multiple factors. Thirdly, the immune power of the individuals studied may differ, thus, toxoplasmosis may lead to different clinical appearances.

Bipolar Disorder

Bipolar disorder (formerly, manic depression) is a chronic disease with a wide range of mood swings. The pathophysiological mechanism is not ascertained yet, though there have been some suggested mechanisms such as synaptic (neurotransmitter-related) and postsynaptic (second-messenger, G-protein, based) mechanisms (18). In addition, there is a genetic tendency among patients with BD.

It has been proposed that infectious agents may cause psychosis directly (via effects on neurons) or indirectly (via immune cells and neurotoxic agents) (19). *Toxoplasma* spp. affects the corticolimbic area, which is involved in impulsivity and aggression in humans (20). Additionally, latent toxoplasmosis has been shown to reduce corticosterone secretion by causing dendritic retraction in basolateral amygdala, this may also contribute to behavioral changes (21).

There are clinical case control studies pointing out a higher prevalence of toxoplasmosis among patients with BD (22,23). In a recent review and meta-analysis, authors concluded that it was not certain if toxoplasmosis could be associated with the symptoms and severity of BD but patients with BD were more likely to be seropositive for toxoplasmosis (24).

Though not certain, there seems to be a link between BD, which may be accepted as extreme mood changes, and toxoplasmosis. More research is necessary to confirm and explain this relationship in detail.

Schizophrenia

Schizophrenia is a devastating neuropsychiatric disease with a lifetime risk of 1% (25). It results in behavioral and cognitive changes in its course. There are many proposed etiological factors, mainly genetic tendency, problems in early neural development -intrauterine environment and early childhood- such as infections, stress, nutritional deficiencies.

The plausible explanations for toxoplasmosis and schizophrenia are several. *Toxoplasma* spp. is a neurotropic parasite, with a special affinity to glial cells (26). The cysts consisting of bradyzoites can be found all over the brain. These cysts may lead to psychological changes by their anatomic location. Apart from its central affinity, toxoplasma leads to some immune cell alterations in the brain as stated in this review many times. Neuroinflammation and upregulation of proinflammatory cytokines cause neural damage (27). *Toxoplasma* spp. uses tryptophan thus, decreased tryptophan -apart from decrease in serotonin production- also causes kynurenic acid, which is a noxious metabolite (28). Additionally, genetic background is known in schizophrenia and also toxoplasmosis (29). All mechanisms help to explain how toxoplasmosis and schizophrenia uses similar pathways, thus may be one of the mechanisms in the multifactorial ground of schizophrenia.

There are two types of clinical data on the association of toxoplasmosis and schizophrenia. First, there are case control

studies showing that high prevalence of seropositivity of toxoplasmosis in patients with schizophrenia. In the meta-analysis of these studies, they analyzed 23 eligible studies out of 42 studies (29). Authors found significantly higher prevalence of toxoplasma antibodies with an OR of 2.7 (95% CI 2.1-3.6, p<0.000001). Second, there are data showing a relation between maternal toxoplasmosis infection and schizophrenia in the child (30,31). It has been shown that children born to mothers with latent toxoplasma infection have more than 2-fold increase of having schizophrenia in later years (29). Nevertheless, the data showing an association of maternal acute infection and schizophrenia in the children, manifested with IgM antibodies during the pregnancy, are still missing. Addition to the data above, there is one more clue that may make us think about the connection between toxoplasmosis and schizophrenia; some of the antipsychotic medications (except valproate) have been shown to inhibit the parasite proliferation in low or moderate degree (32).

Although these are plausible pathways, there is a need for more clinical trials to uncover the mystery of association between toxoplasmosis and schizophrenia.

Obsessive Compulsive Disorder

Obsessive compulsive disorder (OCD) is a neuropsychiatric disorder with both obsessive thoughts and compulsive behavior. It has a multifactorial etiology: genetic, psychological and external factors (learning) may play a role. Other mental disorders such as depression, schizophrenia, bipolar disorder or anxiety disorders may render OCD. Although the pathogenesis is complex, gamma aminobutyric acid (GABA) and serotonin systems are shown to be involved (33). Chronic toxoplasmosis has a profound effect on neurotransmitters. This may explain the association -if there is any- between toxoplasmosis and OCD.

There is little information on the link between toxoplasmosis and OCD in the literature. In the analysis, a recent meta-analysis consisting of eligible 11 studies revealed a positive correlation between prevalence of toxoplasma antibodies and OCD, with an OR of 1.96 (95% CI 1.32-2.9) (34). However, a compulsion such as often hand-washing may be protective rather than acquiring the infection. More clinical trials are needed to clarify this contrariety.

Parkinson's Disease

After AD, Parkinson's disease (PD) is the second most common chronic neurodegenerative disease with an estimated lifetime risk of 3-7% (35). It was first described in the 1800's by James Parkinson and referred to as "shaking palsy" (36). Genetics account for 60% of the pathophysiology of the disease. The rest may be explained by environmental or life-style factors. Whatever the etiologic factor is the hallmark of PD is alpha-synuclein-containing intracytoplasmic eosinophilic inclusion bodies (Lewy bodies) in throughout the brain and degeneration of neurons in the substantia nigra pars compacta leading to dopaminergic deficiency (37).

Toxoplasma spp. adversely affects dopaminergic neurons via increased pro-inflammatory substances such as cytokines. Even in the later stages of the chronic disease, *Toxoplasma* spp. produce tyrosine hydroxylase and this enzyme causes a limitation in dopamine synthesis and dopamine deficiency may be associated with PD. However, pooled data in a recent review did not support the clinical association between toxoplasmosis and PD (38). Nevertheless, there is still a need for future clinical and laboratory studies to investigate the possible link to clarify the issue.

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system and it may cause a major disability especially in young adults. Although the exact etiopathogenetic mechanism is not yet certain, immunologic, environmental, genetic factors have been accused. Additionally, it has been suggested that the prevalence of MS and high level of sanitation in childhood are positively correlated (39). In medical literature this phenomenon was later introduced as the "hygiene hypothesis" by Strachan (40).

Data on the association of toxoplasmosis and MS are unlike other neuropsychological problems. In their study, Stascheit et al. (41) have looked at the seropositivity of toxoplasmosis among patients with MS and age-matched controls. They found a negative association between *Toxoplasma* seropositivity and MS. Previous case-control studies have also demonstrated a protective effect of owning a cat against MS (42,43). In another study, although seropositivity for toxoplasmosis was less among 50 MS patients when compared with 50 family members (as controls), the difference was not reached significance (p=0.09). In a recent meta-analysis of 5 eligible research, OR of toxoplasma seropositivity in patients with MS when compared with controls was 0.72 (95% CI 0.49-1.06) (44). Although this review also suggested no significant association between toxoplasmosis and MS, the findings should carefully be assessed. First of all, there are differences between included studies in terms of the methods used to investigate seropositivity, for instance, some used enzyme-linked immunosorbent assay, others used chemiluminescent immunoassay and enzyme immunoassay. There may also be other factors out such as differences in the investigated population. An additional issue is that, as the authors pointed out, there may be both positive and negative impacts of toxoplasmosis which may be explained by immunity of the parasite.

In sum, despite the conflicting data, we may at least say "a trend" towards inverse association between toxoplasma seropositivity and MS was demonstrated. Further studies will shed more light on this unclear issue.

Autism

Autism or in broader sense autistic spectrum disorder is the developmental disability that causes behavioral change -such as communication and learning differences- leading to social adjustment problems. It is accepted as a multifactorial problem: genetic, environmental, biologic factors may play a role (45).

The underlying mechanism is not clear. However, there are 2 main proposed grounds for the relationship between toxoplasmosis and autism; one experimental study showed a clear relationship between toxoplasma infection and gluten antibody (46). Anti-gluten antibody leads to gluten sensitivity and may end up with various neuropsychiatric diseases including autism. Another mechanism may be persistent neuroinflammation caused by chronic toxoplasmosis in the brain resulting in increased oxidative stress and decreased activity of several enzymes leading to abnormal metabolism of environmental factors and in turn conduce toward autism (47). Recent review concluded that up until now, there is no solid data for the link between gluten and autism (48). Thus, until the cause and effect relationship is

established, it is difficult to designate "toxoplasmosis" as a reason for autism.

Depression and Suicide

As mentioned earlier, there is enough evidence to show that toxoplasmosis may cause behavioral changes. When we talk about the relationship between toxoplasmosis and "depression and/or suicide", though the exact underlying mechanism for these is difficult to uncover, there are four suggested "plausible" factors. Firstly, there are morphological changes accompanying cerebral toxoplasmosis. In mice, scattered cystic lesions of acute toxoplasmosis in the brain have been shown (49). If this finding can be extrapolated, there may be a suggestion that such small cysts might change behavior in humans as well. Secondly, in toxoplasmosis, altered neurotransmitter signaling has been shown. Tryptophan catabolic shunt and serotonin during the reactivation stage of *T. gondii* infection may contribute to the development of depressive-like behavior (50). Last but not least, there is the Altered Immune Response (increased pro-inflammatory signaling) in toxoplasmosis. It has already been known that the sympathetic nervous system operates on the immune function in sickness behavior including major depression (51). Many reports have pointed out the increased blood and cerebrospinal fluid (CSF) levels of pro-inflammatory cytokines, chemokines, adhesion molecules in patients with major depression (52,53). One more factor may be the Medication used for psychiatric disorders; Antipsychotic drugs that block Dopamine (2) receptors may lead to depressive symptoms (54).

Although solid proof of a relationship is not clear yet, the link between toxoplasmosis and depression has long been proposed. There are some studies showing that incidence of toxoplasmosis is higher in depressed patients (55,56). Even more, Kar and Misra reported that their case with the diagnosis of depression responded to antidepressant treatment only after adequate treatment for toxoplasmosis (57).

However, in a recent, detailed meta-analysis of 29 studies revealed that there was no link between major depressive disorder and toxoplasmosis (58). As the authors concluded, there is a need for further well-designed studies to clear the blurred link between toxoplasmosis and all different types of depression.

According to one World Health Organization report, approximately 800,000 people die to suicide each year, with the estimation of a loss of one person in every 40 seconds (59). Depression plays a role in suicide attempts in more than half of the cases (60). The very first report suggesting a link between toxoplasmosis seropositivity and suicide was reported by Arling et al. (61). They have found higher toxoplasma antibody levels in individuals with suicidal attempts when compared with healthy controls. Other reports followed and supported this preliminary report (62,63). In a recent study by Bak et al. (64), seroprevalance of toxoplasmosis among 155 suicide attempters was found higher when compared with 135 healthy controls. More studies will elucidate this interesting link between toxoplasma infection and suicide attempt. In this context, we may suggest a future investigation for toxoplasmosis in patients with depression.

Epilepsy

Epilepsy is a neurological disease that is manifested in a large spectrum of clinical symptoms. Estimated lifetime risk of epilepsy is 7.6 per 1000 persons (65). It may be due to different pathophysiological factors such as trauma, tumors, infections. Etiological factors can be classified as genetic, structural/metabolic and idiopathic (66). If there is no obvious cause found, it is termed as cryptogenic epilepsy.

There are case-control studies showing higher prevalence of seropositivity for toxoplasmosis in patients with cryptogenic epilepsy (67,68). Whereas, in another study, authors found similar seropositivity in 100 patients with cryptogenic epilepsy and 50 healthy controls (69). However, in a recent systematic review and meta-analysis of 6 eligible studies, it was found an OR of 2.25 (95% CI 1.27-3.9) (70). The authors concluded that toxoplasmosis is a risk factor for epilepsy. This data is important when searching for an underlying mechanism for epilepsy especially in toxoplasmosis prevalent areas.

Pathophysiology of epilepsy related to toxoplasmosis is difficult to fully explain. However, there are some suggested mechanisms. Toxoplasma may exert its effect in the brain, which is mostly its primary target, in various ways (71). It affects neurons as well as astrocytes and microglial cells (72). Neurons are more vulnerable, because the latter cells may protect themselves due to their -to a certain level- capability to inhibit the parasite upon its arrival. In latent (chronic) infection with toxoplasma, parasites transform themselves into bradyzoite form and make brain tissue cysts. Location of toxoplasma can be anywhere in the brain but predominantly grey matter, amygdala, hippocampus, and basal ganglia are affected the most. The cyst wall may rupture and disseminate the bradyzoites leading to more microcysts. This process causes inflammatory changes and eventually scars. These foci may be one of the underlying mechanisms of epileptic seizures. Secondly, *Toxoplasma* spp. may affect excitability of the neurons especially in two ways; increased glutamate -the main excitatory amino acid in the brain-, and calcium ion consumption -toxoplasma use the ion for their motility and invasion-. Third possible mechanism for explaining the link between toxoplasma and seizures is the effects on neurotransmitters, including serotonin, tyrosine, glutamate, GABA. *Toxoplasma* spp. uses tryptophan for itself. This will cause depletion of serotonin leading to altered GABA ergic signaling. GABA is an important inhibitory amino acid. It is released by the dendritic cells due to the response to invasion by tachyzoites, in turn leading to a decrease in GABA (73).

Although the plausible mechanisms and meta-analysis stated above, there is a need for more clinical studies to yield a strong data between toxoplasmosis and epilepsy.

Headache/Migraine

Cerebral toxoplasmosis may be manifested by chronic headaches. There are some plausible mechanisms that may explain this association. One case control study showed higher prevalence of toxoplasma seropositivity among patients with migraine (4.24%) compared with healthy controls (26%) and patients with rhinosinusitis (24%) (74). The underlying mechanism may be inflammation -especially by proinflammatory substances- nitric oxide and vascular CSF obstruction and intracranial pressure (75,76). However, clinical data on headache is scarce. Thus, there is a need for well-designed studies on this issue.

There are also some interesting reports about toxoplasmosis. One example is an experimental study showing chronic cachexia in mice infected with toxoplasma (77). Such a link may be due to immunometabolic effects of the parasite. The other suggested

involvement is brain carcinoma; toxoplasmosis prevalence was found increased in patients with brain carcinoma (78). The proposed mechanism was altered microRNA mechanism of the host. It may also be "repetitive tissue trauma" with the rupture and dissemination of the microcysts in the brain.

Conclusion

The field of investigating the association between toxoplasmosis and neuropsychological diseases is fascinating. It resembles that toxoplasmosis has a multifaceted parasitological disease; if human as an "accidental intermediate host" is immunologically strong, *Toxoplasma* spp. can insidiously step back and mimic as if it is friendly, whereas when humans are weak toxoplasma affects their "central control room", namely the brain. We need more studies to lead us how to be strong against toxoplasmosis.

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