The Effect of *Toxoplasma gondii* Parasite on Patients With Schizophrenia: A Review

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ABSTRACT

Background : One of the most prevalent intracellular protozoan parasites, is *Toxoplasma gondii*, which can infect humans as well as a variety of mammals and is the main cause of toxoplasmosis. During the acute stage, the parasite infects numerous organs, and it then selectively creates cysts in the brain, which causes many psychological disorders, including schizophrenia.

Aim of the study : This review's objective is to shed light on toxoplasmosis caused by the *T. gondii* parasite and its association with neurological disorders, such as schizophrenia.

Conclusion : Numerous studies indicate that *T. gondii,* once localized in the brain, can increase the amount of dopamine that is available for processing motivation and pleasure.

Certain alterations in the chemical messengers are employed by the connection between neurons in the brain.

It was shown that schizophrenia, depression, suicide attempts, and other neuropsychiatric disorders are all related to seropositivity for the intracellular parasite, *T. gondii*.

Keywords : *T. gondii* , Toxoplasmosis , Schizophrenia .

تأثير المقوسة الكوندية على مرضى الفصام : مراجعة

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الخلاصة

الخلفية : يعتبر طفيل المقوسة الكوندية *T.gondii* واحد من اكثر الطفيليات الاولية انتشارا داخل الخلايا والذي يمكن ان يصيب الانسان وكذلك مجموعة متنوعة من الثديات وهو السبب الرئيسي لداء المقوسات (داء القطط), حيث يصيب الطفيلي العديد من الاعضاء خلال المرحلة الحادة, وقد يشكل الطفيل اكياس داخل الدماغ بشكل تفضيلي مما يسبب اضطرابات نفسية عديدة منها الفصام.

هدف الدراسة : الهدف من هذه المراجعة القاء الضوء على داء المقوسات الذي يسببه طفيل المقوسة الكوندية وارتباطه بالاضطرابات العصبية مثل الفصام

الاستنتاج : تشير عدد من الدراسات الى ان طفيل المقوسة الكوندية بمجرد توطينه في الدماغ , يمكن ان يعزز توافر الدوبامين وهو ناق عصبي ضروري لمعالجة التحفيز والسرور.

كما تحدث تغييرات معينة في النواقل الكيميائية التي تستخدمها الوصلات بين الخلايا العصبية في الدماغ بسبب الاصابة المزمنة بالمقوسة الكوندية.

لقد وجد ان الفصام ,محاولة الانتحار, الاكتئاب والحالات العصبية الاخرى كلها مرتبطة بالايجابية المصلية لطفيل المقوسة الكوندية داخل الخلايا.

الكلمات المفتاحية : المقوسة الكوندية ، داء المقوسات (داء القطط) ، مرض الفصام .

INTRODUCTION

One of the most frequent intracellular infections is *Toxoplasma gondii.* It can infect people as well as a number of mammals and birds[1,2]. Uncooked meat that has cysts on it or oocysts that have been ingested through contaminated water, soil, or food are the main causes of Toxoplasmosis.

T. gondii goes through two stages in its life: the sexual phase or the enter epithelial cycle, which occurs in cats only; and the asexual phase, or the extraintestial cycle, which occurs in cats and intermediate hosts of mammals, including humans and birds as shown in fig.(1)[3, 4].

According to socioeconomic and health conditions, the occurrence of this parasite varies from one country to the next [5].

Humans can contract toxoplasmosis, a disease spread by food, primarily by eating meat that contains tissue cysts. Infection is increasing, especially in ruminants, birds, and pigs, are on the rise, likely due to widespread environmental contamination by oocysts shed by cats (domestic or wild) [6].

Since toxoplasmosis is an opportunistic illness, roughly 80% of first infections are asymptomatic as a result of the host immune system's successful management of the condition, manifesting only as a brief illness with lymphadenopathy, fever, lethargy, and headache [7].

The parasite's primary infection of pregnant mothers causes serious congenital infections in fetuses and newborns. *T. gondii* can harm the brain and spinal cord in immunocompromised people (immunosuppressive medicines, HIV infection), or it can mimic pulmonary toxoplasmosis or disseminated infection. In healthy people, toxoplasmosis typically has no noticeable symptoms; nonetheless, modest cervical or axillary lymphadenopathy or symptoms that could be appendicitis or ocular infection have been recorded in immunocompetent individuals. Recent studies have suggested possible associations between toxoplasmosis and rheumatoid arthritis, depression, schizophrenia, and suicide [8, 9].

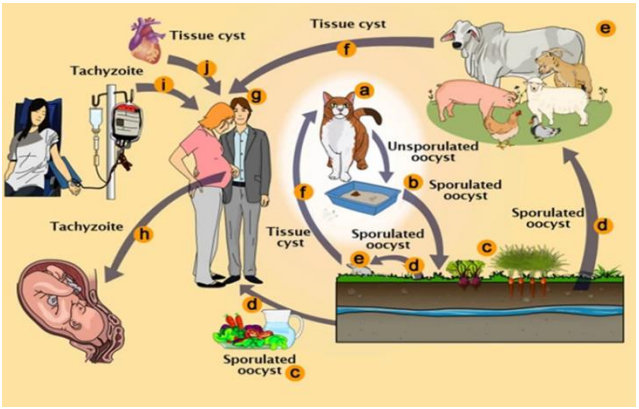

Fig. (1). Routes of transmission for *T. gondii*. a: feline-specific host (a cat). b: Cat feces contain unsporulated oocysts, that have been sporulated in food. c: shrubs. d: Intermediate hosts may consume oocyst. e: host intermediate. f: consumption of tissue cysts found in raw beef. Host intermediate (human) .Tachyzoites spread to the fetus through the placenta. I: Transmission via organ donation and blood transfusion (j) [4].

Effect of Toxoplasmosis on The Brain

Ingestion of tissue cysts, oocysts, or tachyzoite infection during pregnancy is three potential methods by which the intracellular protozoan parasite *T. gondii* might infect humans. During the acute phase, tachyzoites travel throughout the body, primarily forming cysts in the brain, where they establish a permanent infection that maintains a delicate balance between the parasite's capacity and the host's immunity to elude the immunity system. Multiple brain cell types, including neurons and astrocytes, are susceptible to infection. Evidence from in vitro studies on cells other than brain cells shows that infection significantly alters host cell gene expression, including substances implicated in immune response support and signal transduction pathways [10].

Chronic infection with *T. gondii* alters the chemical messengers utilized by inter-neuronal connections in the brain. The enzyme that slows down the production of dopamine [11] is encoded by the amino acid hydroxylase gene, which is extremely similar to two loci in the *T. gondii* genome. This likeness suggests that this parasite, if established in the brain, can increase levels of the neurotransmitter dopamine, which is critical for the regulation of reward and motivation [12, 13]. It's noteworthy that *T. gondii* behavioral effects can be reversed by drugs that prevent dopamine metabolism[14].

The primary immune response mediator required to keep *T. gondii* in check in the brain and preserve the chronic infection's latent state is

interferon-c. Additionally, microglia, astrocytes, and neurons produce a wide range of cytokines in response to infection, which can either stimulate or decrease inflammatory responses. Parasite-host equilibrium and infection progression are affected by some factors, including the strain's genotype, the parasite's life cycle stage (tachyzoite, cyst, or oocyst), and the host's immune response. Tachyzoites penetrate microglia, astrocytes, and neurons, according to in vitro experiments utilizing mouse brain cells. The parasite then develops cysts inside these cells. *T. gondii* also produces cysts in human neurons and astrocytes, according to an in vitro investigation using these cells [15].

The glial cells of a patient with toxoplasmic encephalitis contained tachyzoites at various stages of development. *T. gondii* bradyzoites were found in a cerebellar Purkinje cell of a patient with toxoplasmic encephalitis[16].

Schizophrenia Associated with *Toxoplasma Gondii*

A ubiquitous neuropsychiatric disorder with an unknown origin that affects 1% of individuals globally is schizophrenia. Patients with schizophrenia displayed negative symptoms such as decreased motivation and slower cognitive processing speed, as well as psychotic illnesses such as delusions, disorganized speech, and hallucinations [17].

It's possible that hereditary factors played a role in the development of schizophrenia due to the increased prevalence of the condition in the children of people with schizophrenia. The surrounding environment is also a major role.

The beginnings of symptoms are typically noticed in late adolescence. Genetic predispositions affecting the immune system and synaptic signaling pathways, along with the environmental factors such as obstetric problems, early social trauma, urban childhood residence, and the use of psychotropic medicines have all been linked to the development of this illness[17, 19].

Many neurotransmitter levels, including dopamine, extracellular glutamate, and the glutamate transporter GLT-1 in astrocytes, have been shown to fluctuate in people with schizophrenia, as reported by Fuglewicz *et al*.[18]. In addition, elevated glutamate levels and reduced hippocampal volume have been observed in patients with schizophrenia. [20].

First-generation antagonist drugs like chlorpromazine and haloperidol are used to inhibit dopamine D1/D2 receptors to treat positive symptoms of schizophrenia [21, 22].

A relationship has been shown between toxoplasmosis and schizophrenia in more recent research conducted in Tunisia [23], France [24], and Denmark [25]. Because the obtained OR (odds ratio) values are higher than those of other genetic and environmental factors that have also been earlier researched for their associations with schizophrenia, the results support the hypothesis that exposure to *T. gondii* is a risk factor for developing schizophrenia [26].

Evidence suggests that infection with tachyzoites from *T. gondii* causes calcium influx in response to glutamate stimulation to become unregulated. Calcium plays a crucial role in the onset and spread of seizure activity[27]. *T. gondii* infection has now been linked to epilepsy in two meta-analyses. Most infections have been found to alter the release of dopamine from the corresponding neurotransmitter systems [28].

Among the abnormalities in neurotransmitter levels seen in patients with schizophrenia are elevations in dopamine, gamma-aminobutyric acid (GABA), and glutamate [29].

Parasite-caused dopamine abnormalities may participate in the development or progression of the disease. Schizophrenia is characterized by a breakdown in the brain's dopaminergic, mesolimbic, and mesocortical circuits that control motivation, emotion, and reinforcement[30]. The immune system may potentially play a role in the suggested link between *T. gondii* and schizophrenia[31]. Through interactions with MHCI alleles on infected cells, CD8+ T lymphocytes (a component of the adaptive immune system) help to keep *T. gondii* infections under control. Infection with other virulent parasite strains, such as the RH may considerably dampen these CD8+ T cell responses [32, 33].

This means that in a population with a low frequency of schizophrenia, seropositivity for *T. gondii* is only associated with a higher risk of developing psychosis in newly diagnosed cases, but not in long-term sufferers[34].

Leweke *et al*. observed that IgG levels of *T. gondii* were considerably lower in patients with schizophrenia. As previously reported[35], certain antipsychotic medications may influence on antibody levels or the persistence of parasites in the brain. The antipsychotics' general immune-suppressive effect may result in decreased antibody levels[36].

T. gondii growth can be directly inhibited in vitro by the use of the mood stabilizer valproic acid and the antipsychotic haloperidol[37].

Additionally, antipsychotic medications may indirectly affect brain homeostasis, which may affect on cyst load. It has been noted that *T. gondii* persistence in the CNS is correlated with increasing levels of dopamine, glutamate, and KYNA, changing neuronal functioning [38].

It is unclear whether the parasite mediates these metabolic modifications by secreted cues, but antipsychotic medications that act on similar pathways might influence *T. gondii*'s ability to remain in the CNS. A greater proportion of *T. gondii* serotypes was found in patients with treatment-resistant forms of schizophrenia compared to those who responded to treatment. This lends credence to the possibility of *T. gondii* and antipsychotic medication interactions [39].

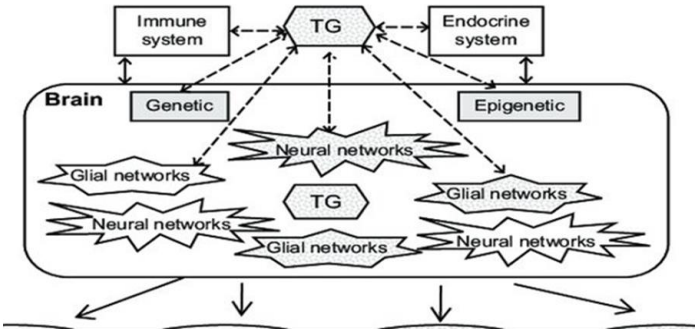

Fig. (2) *T.gondii* infection's effects on the brain and its fundamental mechanisms for generating behavior [40].

Although a substantial correlation between parasitism and schizophrenia has been noted, these investigations do not support the theory that parasitism is an infectious cause of schizophrenia, and no causative link has been established. Schizophrenics' disturbing behavior, unpredictable lifestyle, and/or disadvantaged socioeconomic conditions may make them more prone to come into contact with *T. gondii*, which could explain positive serological results [41].

Studies in cell culture have revealed that glial cells, particularly astrocytes, are specifically harmed from a neuropathological perspective in infected patients [42]. Numerous glial abnormalities, such as decreased astrocyte counts, have also been observed in postmortem examinations of schizophrenia brains [43]. Similar to how humans with schizophrenia are known to have low levels of dopamine, norepinephrine, and other neurotransmitters, animal investigations of *T.* infections have shown that this bacterium impacts these levels as well.

Higher levels of impulsivity in males and increased human trait hostility in females have both been linked to latent *T. gondii* infection [44]. Suicide attempts are more common among people with high levels of *T. gondii* antibodies, according to another research [45]. *T. gondii* antibody titers have been demonstrated to be positively correlated with national homicide and suicide rates in cross-national studies, supporting the findings of the aforementioned individual-level research [46].

Another study found that there was a higher rate of seropositivity among prisoners than among controls [47]. According to further reports, both fatal and non-fatal automobile accidents are related to *T.gondii* seropositivity, which is likely due to decreased impulse control [48].

CONCLUSION

Schizophrenia is a chronic disease, its causes are unknown, and the patient is characterized by changes in feelings and behavior. Several studies have shown the relationship between Toxoplasma one of the causes of schizophrenia. Where the proportion of antibodies to *T. gondii* increases, which destroys the astrocyte cells in the brain, as occurs in cases of schizophrenia. As this parasite works to cause changes in chemical messages between neuronal connections, and the localization of *T. gondii* in the brain enhances the existence of dopamine, a neurotransmitter necessary to stimulate pleasure and motivation. *T. gondii* toxoplasmosis has been connected to a wide range of mental health issues, including clinical depression and suicide attempts.

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