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Review Article

Toxoplasma gondii: A Probable Cause of Alzheimer's Disease

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ABSTRACT

Toxoplasma gondii is an intracellular parasite that belongs to the Apicomplexa phylum. It is known for causing a disease called toxoplasmosis in both humans and a variety of mammals. In its acute phase, the parasite exhibits a striking ability to invade multiple internal organs including the brain, and eventually forming long-lasting cysts in the infected organs. These cysts are associated with an increased risk of neurological disorders, such as Alzheimer's disease. The researches have shown that central nervous system (CNS) toxoplasmosis is capable of disrupting the normal neural processes via mechanisms like inflammation, immune response dysregulation, and neuronal damage. These disruptions may not only accelerate neurodegenerative conditions but they can also lead to expedite existing vulnerabilities in brain function. The relationship between *T. gondii* infection and Alzheimer's has not been fully understood, however, multiple studies have supported the role of CNS toxoplasmosis on various neurological pathologies.

Keyword: Parasites, *Toxoplasma gondii*, Toxoplasmosis, Alzheimer's disease .

INTRODUCTION

Toxoplasma gondii is considered one of the most prevalent infections and is categorized as a neurotropic parasite. It is an obligate intracellular protozoan parasite that belongs to the Apicomplexa phylum and demonstrates remarkable transmissibility. *T. gondii* can cause permanent and life long infections in numerous warm-blooded animals including humans which represent the intermediate hosts of this parasite, while felines are considered as definitive hosts. Approximately one-third of the global human population carries this infection. However, the infection rates of *Toxoplasma* parasites vary considerably (1-90%) across different countries depending on cultural practices, social factors, and geographic location (Rostami *et al*., 2016, 2017).

Transmission typically takes place via several pathways, consumption of undercooked meat containing tissue cysts, ingestion of food or water contaminated with sporulated oocysts from infected cat feces, vertical transmission from mother to fetus across the placenta, and transplantation of infected organs or by transferring blood from infected person to another (Motoya *et al*., 2005; Mahmoudvand *et al*., 2015).

The rate of parasites' spread and persistence in human hosts depends on host immune responses, where the immune reactions can either prevent parasite-induced damage or facilitate *T. gondii*-associated immunopathology (Yermakov *et al*., 1982). Infection with *T. gondii* range from asymptomatic to severe illness, which affects lymph nodes, eyes, and the central nervous system (Dubey, 2004). In most immunocompetent individuals, acute or latent *T. gondii* infection presents with no clinical manifestations or only minor symptoms such as illness, lymph node enlargement, and fever (Schlüter and Barragan, 2019).

Toxoplasmosis poses particular risks in immunocompromised individuals (with primary or secondary immune deficiencies), organ transplant recipients, and pregnant women due to its opportunistic characteristics. In these populations, the infection frequently becomes symptomatic and fatal, particularly when involving the CNS, one of the most commonly affected organs due to its immune-privileged status that allows *T. gondii* to evade immune detection (Yermakov *et al*., 1982; Coelho *et al*., 2003; Jones *et al*., 2003). Pregnant women face special risks as initial exposure can cause serious illness or even fatality to the developing fetus. Parasite transmission from mother to fetus during the first trimester of pregnancy may result in brain injury, eye tissue damage, or fetal death (Wallon and Peyron, 2018).

During acute infection, tachyzoites can evade the immune system, leading to tissue cyst formation containing bradyzoites in various organs including the liver, lungs, muscles, and lymph nodes, with a tendency to establish in brain tissue (Montoya and Liesenfeld, 2004; Wilson and Hunter, 2004). In the CNS, *T. gondii* cysts can alter neuronal cell biology during latent infection, affecting neurotransmitter production, signal transmission, synapse development, and branching of dendritic cells (Prandovszky *et al*., 2011; Gatkowska *et al*., 2013).

Life cycle

T. gondii has a distinctive lifecycle that includes both asexual and sexual reproduction phases. The parasite exists in three infectious forms; a rapidly proliferating form known as tachyzoites, a slowly proliferating form found in tissue cysts known as bradyzoites and a form encased by oocysts (infectious stage) which exists in the intestines of infected cats known as sporozoites. These stages interconnect within a complex lifecycle which includes various levels of differentiation which are required for the parasite to persist within its various hosts (Dubey *et al*., 1998).

Coccidian parasite such as *Toxoplasma gondii* within the intestinal tract of cats which are the definitive hosts undergoes both asexual and sexual reproduction. When the definitive host acquires the parasite via consumption of food/water containing oocysts or via consuming meat containing tissue cysts. Sporozoites or bradyzoites then invade the intestinal epithelium, transform into rapidly growing tachyzoites, and spread throughout the body (Sinai *et al*., 2020). In the small intestine, bradyzoites invades the epithelial cells of the villi. The bradyzoites then transition into the merozoite stage which undergoes asexual then sexual proliferation inside epithelium of the intestine. The rapid

turnover of the intestinal epithelium necessitates that parasites finish their development prior to being shed off (Hutchison *et al*., 1971).

Sexual phase

Following numerous asexual cycles, the merozoites differentiates to male or female gametocytes known as microgametocyte and macrogametocyte respectively, which indicates the initiation of sexual development phase, this phase occurs only in the feline hosts. The process that starts the transitioning of the parasite from asexual to sexual phases is yet to be identified, as are the characteristics that pinpoint the merozoites that will evolve into sexual gametes (Ferguson and Dubremetz, 2020).

The sexual cycle in feline hosts progresses with macrogamete and microgamete production throughout the small intestine. Fertilization of these gametes produces zygotes and is followed by the development of oocysts that are surrounded by a distinctive wall providing physical protection and chemical resistance against environmental challenges (Belli *et al*., 2006; Dubey, 1998). Through feline feces, the oocysts are then released into the environment. Even infection by a single parasite can result in massive oocyst shedding millions per cat during a period of 7-15 days (Dubey, 2001).

The release of oocysts leads to an aerobic development process known as sporulation, which is necessary for them to become infectious. This process typically takes approximately seven days with temperatures of 20-25 ℃, leading to the production of two sporocysts (each one containing four sporozoites) withing a single oocyst (Dubey, 1998). Only the oocyst is able to develop without any host, and because of their high resistance, the oocysts can persist for a long time in soil and water. Humans can be infected consumption of oocysts contaminated food or water.

Intermediate hosts may also get infected by consuming undercooked meat that contains bradyzoites within tissue cysts. The ability of these bradyzoites to tolerate high acidity and trypsin enzyme lysis explains their role in transmitting the infection by consumption of tissue cysts. The cyst wall is not strong enough to resist the digestive enzymes and lyse when exposed to trypsin, in contrast the bradyzoites are able to persist in such environment and infect the host (Roberts *et al*., 2012).

Infection routes

As mentioned before, humans can be infected via consumption of contaminated food and water. In the small intestine, the released sporozoites or bradyzoites infect the epithelium. These forms rapidly develop into tachyzoites the parasitic forms responsible for most of the manifestations and the acute phase of the infection. While tachyzoites can develop in any nucleated cell, *T. gondii* bradyzoites and tissue cysts have a preference to immune-privileged organs such as muscles, eyes, heart, or brain (Cabral *et al*., 2016). The ability of bradyzoites to withstand the immunity and common medications is the cause of chronic infection (Tu *et al*., 2018), additionally, their ability to revert to the rapidly proliferating form (tachyzoites) also contributes to their chronicity. Vertical transmission of tachyzoites from mothers to fetuses represents another infection pathway in humans and other intermediate hosts.

CNS toxoplasmosis

The central nervous system is considered an immune privilege system with numerous mechanisms maintaining its immunological and pharmaceutical advantages (Muldoon *et al*., 2013; Engelhardt and Sorokin, 2009). One of these mechanisms being the blood brain barrier (BBB) which separates the CNS from systemic circulation, which leads to the limitation of immune cells and inflammatory mediators. Additionally, the CNS lacks standard connections to the lymphatic system components with limited number of dendritic cells in its parenchyma, all of these factors assist the neurotropic parasites to evade immunity. Nevertheless, immune cell trafficking into the CNS may significantly increase during infection or severe disease status (Wilson *et al*., 2010).

During acute toxoplasmosis, tachyzoites can evade immune responses, resulting in tissue cysts formation containing bradyzoites, particularly in the brain. CNS infection by *T. gondii* requires parasite invasion that circumvents host immune responses and overcomes protective barriers like the blood brain barrier. The metabolically active tachyzoites reside within host cells in parasitophorous vacuoles and can travel through the bloodstreams to penetrate the CNS via infected white blood cells.

After exiting these WBCs, one of the ways these parasites access neuronal tissue is by penetrating cellular junctures and via transcytosis allowing them to migrate across the endothelium. *T. gondii* reproduction may decrease substantially after CNS entry, but bradyzoites typically survive in a state of quiescence throughout the host's life (Adalid-Peralta *et al*., 2018; Barragan and Sibley, 2003; Lambert and Barragan, 2010).

During latent CNS infection, *T. gondii* cysts can alter neuronal cell function, affecting neurotransmitter production, signal transmission, neural synapse development, and neuromorphic dendritic architecture. Previous research demonstrates that *T. gondii* in the central nervous system induces the innate immune system as well as the adaptive immune system mediated by T-helper cells type 1, this action leads to the release of certain inflammatory markers like Tumor Necrosis Factor alpha, Interleukin 1, and Interleukin 6, as well as an intercellular messenger nitric oxide, these have protective role in the immune system however they are also produce some pathological effects in the brain tissue (Liesenfeld *et al*., 2011; Munoz *et al*., 2011). Although these factors causes limitation in multiplication and spread of *T. gondii*, but also healthy neuronal tissue and function can be affected by these inflammatory responses and sustain significant damage that disrupts neurotransmitter and synapses functioning (Dunn, 2006; McCusker and Kelley, 2013; Saito *et al*., 1991).

Previous investigations revealed that neuronal degeneration caused by the inflammatory response in the CNS serves a crucial role in the etiology of chronic neuronal pathologies especially ones that are degenerative in nature like Alzhiemer's disease (Heneka *et al*., 2010). Several studies indicate that chronic toxoplasma infection may contribute to obsessive-compulsive disorder, cognitive dysfunctions, cryptogenic epilepsy, headaches, and schizophrenia development (Miman *et al*., 2010; Torrey *et al*., 2007; Al-Ardi, 2021). Furthermore, *T. gondii* infection might induce behavioral changes through multiple mechanisms: where the parasite itself can cause additional infection, severe neuronal tissue injury, *T. gondii* can also alter the pathologies of concurrent infectious, or the interaction between these elements (Hermes *et al*., 2008).

IFN-γ, the primary cytokine regulating immune defense against *T. gondii*, is essential in all infected tissues, including the CNS. However, IFN-γ-activated microglia can trigger tissue damage by producing toxic metabolites such as NO, a powerful stimulant of central nervous system diseases associated with inflammatory neuronal abnormalities (Rozenfeld *et al*., 2005). IFN-γ also causes degeneration in dopamine-producing neurons (Çelik *et al*., 2010). Furthermore, the infection can induce the action of tyrosine hydrolase which in turn enhances the synthesis of dopamine (Bouscaren *et al*., 2018). Consequently, this parasite potentially represents a major causative organism that is associated with neurodegenerative conditions including Alzheimer’s disease (Mahami-Oskouei *et al*., 2016).

Alzheimer’s pathology

Dementia represents a widespread neurological condition characterized by declining of cognitive function, emotional changes, language expression difficulties, and reduced motivation (American Psychiatric Association, 1994). It is considered one of the most common etiologies of dementia is a slow progressing neurological condition. In industrialized nations, Alzheimer's prevalence reaches approximately 7% in people over age 65 and 40% in those over age 80 (Perry *et al*., 2016; Dalimi and Abdoli, 2012; Rashno *et al*., 2016).

The pathophysiology of Alzheimer's disease is characterized by obvious neurodegeneration which is mainly mediated by key features including neuritic plaques and neurofibrillary tangles, βeta amyloid is the principal constituent of these plaques, consisiting of 40 to 42 amino acids that are produced via the proteolytic cleavage of the amyloid precursor protein APP. It has been suggested that the abnormal accumulation of the beta amyloid plaques is the main culprit causing the death of selectively vulnerable neurons, the second factor is the formation of the neurofibrillary tangles which consist of hyperphosphorylated tau protein and ubiquitin, all of these are considered the hallmarks of AD (Kalia and Lang, 2015). Current experimental evidence shows these factors are responsible of a vicious cycle that drives the development of this AD (Griffin *et al*., 1998; Griffin *et al*., 2000).

The risk factors that are associated with progression of Alzheimer's disease include age, Aβ and tau protein accumulation, in addition to genetic factors, family history, cardiovascular risk factors (Querfurth and LaFerla, 2010; Berkris *et al*., 2010; De Bruijin and Ikram, 2014; Souza *et al*., 2018), and numerous infectious agents including bacteria (*C.pneumoniae, H.pylori, B.burgdorferi*), viruses (CMV, HSV I), and parasites like *T. gondii* (Bu *et al*., 2015; Mahami-Oskouei *et al*., 2016).

Conclusion

Toxoplasma gondii is a highly transmissible, neurotropic obligate intracellular parasite that leads to the formation of long-term tissue cysts in immune-privileged organs, notably the brain. In the CNS, it forms latent cysts and those combined with host immune response alter neuronal biology, disrupt neurotransmitter metabolism and synaptic structure, and cause chronic inflammation driven by cytokines such as IFN-γ, TNF-α, IL-1, and IL-6. These processes can damage neurons directly and indirectly. T. gondii infection does not by itself fully explain Alzheimer's disease but constitutes a plausible, infection-related risk factor that can accelerate or exacerbate already existing neurodegenerative processes, we theortize this because neuroinflammation and neuronal degeneration are central features in Alzheimer's disease pathology, and because chronic T. gondii infection produces the same types of inflammatory and neurochemical disturbances, however, more extensive research into the relationship between Alzheimer's disease and T. gondii must be made to absoulitly confirm it.

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داء المقوسات الغوندية: سبب محتمل لمرض الزهايمر

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الملخص

تُعدّ المقوسات الغوندية، إحدى أكثر الطفيليات الأولية داخل الخلوية شيوعًا تنتمي الى شعبة معقدات القمة، وتُعتبر المسبب الرئيسي لداء المقوسات في الانسان ومجموعة متنوعة من الثدييات. خلال المرحلة الحادة، يقوم الطفيلي بإصابة عدة أعضاء داخلية بضمنها الدماغ قبل أن يشكل أكياسًا انتقائية طويلة الامد. وقد تبيّن أن هذه الأكياس مرتبطة بزيادة خطر الإصابة بالاضطرابات العصبية، بما في ذلك مرض الزهايمر. أظهرت الأبحاث أن داء المقوسات في الجهاز العصبي المركزي (CNS) يمكن أن يخلّ بالتفاعلات العصبية الطبيعية من خلال آليات متعدده مثل الالتهاب، واضطراب الاستجابة المناعية، وتلف الأعصاب. لا تقتصر هذه الاضطرابات على تسريع الحالات التنكسية العصبية فحسب، بل قد تزيد أيضًا من تفاقم الحالات المرضية الموجودة في وظائف الدماغ. وعلى الرغم من أن العلاقة بين الإصابة بداء المقوسات ومرض ألزهايمر غير مفهومة، إلا أن العديد من الدراسات تدعم دور داء المقوسات في الجهاز العصبي المركزي في التسبب بمختلف الأمراض العصبية.

الكلمات الدالة: طفيليات، المقوسات الكوندية، داء المقوسات الكوندية ، مرض الزهايمر.