Stallion Journal for Multidisciplinary Associated Research Studies
ISSN (Online): 2583-3340
Volume-3 Issue-4 || August 2024 || PP. 1-10 https://doi.org/10.55544/sjmars.3.4.1

Article Review: Relationship between Toxoplasmosis and other Diseases

May Y. Al-ma'amouri[1] and Mohammed Jasim Shakir[2]
[1]Medical Technology Institute-Almansour, Middle Technical University, IRAQ.
[2]Department of Microbiology, College of Medicine, Univercity of Diyala, Diyala, IRAQ.

[1]Corresponding Author: may_yahya@mtu.edu.iq

www.sjmars.com || Vol. 3 No. 4 (2024): August Issue

Date of Submission: 25-07-2024	**Date of Acceptance:** 29-07-2024	**Date of Publication:** 13-08-2024

ABSTRACT

Water provision is sensitive to climate change, and agricultural production and food supply are sensitive to water availability. Water scarcity affects food security and agricultural economic development through changes in agricultural production and changes in the composition of produced goods. Recent droughts also led to a decrease in the volume of water allocated to agriculture, which led to a decrease in total agricultural production and exports, and this has subsequent impacts on food security and economic development. The research aimed to measure the impact of water scarcity on agricultural economic development for the period 1990-2022. The research included three behavioral equations with three endogenous variables: the cultivated area, the value of agricultural output, and the value of gross domestic product, and four exogenous variables: the amount of available water, agricultural labor, and the value of agricultural investments and the income of other sectors, the studied model is called the sequential model, which was estimated using the Recursive method, using the ordinary least squares (OLS) method. The results indicated that increasing the amount of available water will lead to an increase in the cultivated areas by 141,129.2 dunums, and that increasing one thousand dunums of the cultivated area will increase agricultural output by 0.00821, and that agricultural labor is inversely proportional to agricultural output. It became clear that if the income of the rest of the sectors increased by one unit, the domestic product would increase by 0.1873. Water scarcity will reduce cultivated areas, which in turn will decrease agricultural output, causing the value of agricultural output to decrease and its contribution to the gross domestic product to decrease. In turn, it will have serious repercussions on agricultural economic development. Therefore, the research recommends the necessity of integrated water management and improving the efficiency of its use, as well as the application of modern technologies in agriculture, such as sprinkler irrigation, hydroponics, and redrawing crop compositions to ensure maximizing the net return per unit of water.

Keywords- climate change, recursive, water security, water management, poverty.

I. INTRODUCTION

Prevalence of human infection with Toxoplasma gondii has been increasing in China due to the increasing number of cats. However, little is known of the epidemiology of T. gondii infection in different cancer patient groups. The prevalence of anti-T. gondii IgG in cancer patients (35.56%) was significantly higher than that in controls (17.44%).

The highest T. gondii seroprevalence was detected in lung cancer patients (60.94%), followed by cervical cancer patients (50%), brain cancer patients (42.31%) and endometrial cancer patients (41.67%). Exposure with soil and consumption of raw/undercooked meat were significantly associated with T. gondii infection in cancer patients. **(7)**

T. gondii infection is a severe problem in cancer patients and it is imperative that improved integrated measures should be conducted to prevent and control T. gondii infection in cancer patients. The protozoan parasite Toxoplasma gondii can infect nearly all warm-blooded animals, including humans. **(1)**

Stallion Journal for Multidisciplinary Associated Research Studies
ISSN (Online): 2583-3340
Volume-3 Issue-4 || August 2024 || PP. 1-10 https://doi.org/10.55544/sjmars.3.4.1

Approximately 30% of the world's population is estimated to be infected with T. gondii. [2] Humans become primarily infected by ingesting raw or undercooked meat containing viable tissue cysts, or by ingesting water or food contaminated with oocysts from infected cat feces. [3]

In healthy humans, the infection with T. gondii is usually asymptomatic, but it can be fatal in the immunocompromised individuals, such as HIV/AIDS patients, cancer patients, and organ transplant recipients. An increased frequency of Toxoplasma encephalitis has been reported in AIDS patients, especially those with significant immunosuppression when CD4 T lymphocyte cell counts is <200 cells/μL, and T. gondii infection is regarded as an important opportunistic pathogen that lead to the death of AIDS patients.

The cancer can also reactivate latent T. gondii infection during antitumor treatment process. A variety of malignancies, including lymphoma, leukemia, and myeloma, can reactivate toxoplasmosis. Transplantation of an organ from seropositive donor can activate latent infection in a seronegative recipient receiving immunotherapy. [4]

Transplantation of an organ from seronegative donor can also initiate fatal infection by activation of the latent infection in a seropositive recipient receiving immunosuppressive therapy. It seems that danger of transplanting an infected organ into a seronegative recipient is greater than that of transplanting a non-infected organ into a seropositive recipient. [5]

Fatal toxoplasmosis has been reported in heart, liver and bone marrow, haematopoietic stem cell transplant recipients. [6]

Toxoplasmosis can be complicated and is considered a serious disease in immunocompromised patients, in which the reactivation of a latent infection can be fatal. The incidence of reactivated toxoplasmosis may rely on the prevalence and concentration of IgG antibodies. [1]

It is necessary to obtain information concerning the prevalence of T. gondii infection in different special populations worldwide. We conducted a global meta-analysis to assess the seroprevalence and odds ratios (ORs) of T. gondii infection in immunocompromised patients compared with those in control individuals.

Toxoplasma gondii (T. gondii) is a prevalent protozoan parasite of medical and veterinary significance. It is the etiologic agent of toxoplasmosis, a neglected disease in which incidence and symptoms differ between patients and regions. In immunocompetent patients, toxoplasmosis manifests as acute and chronic forms. Acute toxoplasmosis presents as mild or asymptomatic disease that evolves, under the host immune response, into a persistent chronic disease in healthy individuals.

Chronic toxoplasmosis establishes as latent tissue cysts in the brain and skeletal muscles. In immunocompromised patients, chronic toxoplasmosis may reactivate, leading to a potentially life-threatening condition. Recently, the association between toxoplasmosis and various diseases has been shown. These span primary neuropathies, behavioral and psychiatric disorders, and different types of cancer.

Toxoplasma gondii (T. gondii) is an obligate intracellular parasite that infects a broad range of animals including approximately one third of the world's human population. [9]

The prevalence of T. gondii infection varies widely between countries. In North America, South East Asia, and Northern Europe, prevalence is low and ranges between 10 and 30%. In Central and Southern Europe, a moderate prevalence is reported and ranges between 30 and 50%, while in Latin America and tropical African countries, a high prevalence is common and reaches an alarming percentage of 80% in certain regions. [1]

The Center for Disease Control and Prevention (CDC) reported that more than 40 million people in the United States are infected with this parasite, and classified toxoplasmosis among the neglected parasitic infections requiring public health action control. [8]

The T. gondii life cycle involves a sexual stage occurring in the intestinal epithelium of felines and an asexual part involving any warm-blooded animal. It exhibits three morphologically distinct infectious stages: tachyzoites (responsible for acute toxoplasmosis leading to tissue damage), bradyzoites (responsible for chronic toxoplasmosis manifested as cysts in the brain and skeletal muscle tissues), and sporozoites (infective forms found in oocysts shed in cats' feces).

Human infection starts following the oral ingestion of sporulated oocysts in food or water contaminated with felines' feces, or upon the ingestion of tissue cysts after the consumption of contaminated raw or undercooked meat. Vertical transmission follows the transplacental spread of tachyzoites from a primo-infected pregnant mother to her fetus/baby, leading to congenital toxoplasmosis.

II. TOXOPLASMA GONDII PATHOGENESIS

The manifestations of toxoplasmosis differ between patients **(Figure 1)**. In the sections below, we will provide an overview on the direct pathogenesis of T. gondii spanning acute, chronic, congenital, and ocular infection and reactivated chronic toxoplasmosis.

Stallion Journal for Multidisciplinary Associated Research Studies
ISSN (Online): 2583-3340
Volume-3 Issue-4 || August 2024 || PP. 1-10 https://doi.org/10.55544/sjmars.3.4.1

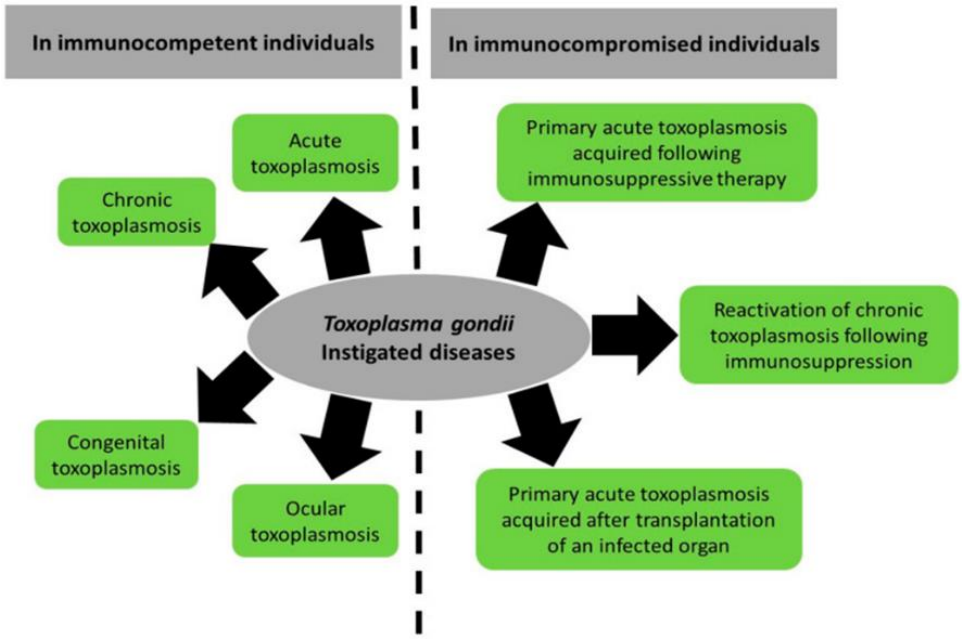

Figure1: Summary of Toxoplasma gondii-induced diseases and their spectrum between immunocompetent and immunocompromised patients.

III. TOXOPLASMOSIS IN IMMUNOCOMPETENT PATIENTS

Acute Toxoplasmosis

Acute toxoplasmosis develops after an incubation period of a few days following tachyzoites' spread and replication. It is asymptomatic in more than 80% of immunocompetent individuals. It can manifest with flu-like symptoms including fever and mononucleosis-like symptoms, with cervical posterior adenopathy, myalgia, and asthenia. [3]

Occasionally, chorioretinitis may occur. The severity of infection is also related to the genotype of the parasite strain. In North America and Europe, six genetic markers were used to group *T. gondii* strains into clonal lineage I, II, and III, with I considered to have the highest virulence in preclinical mouse models, II less virulence, and III considered to be avirulent . In French Guiana and Latin America, atypical strains showed high genetic diversity and represented a severe acquired toxoplasmosis among immunocompetent individuals. These subjects developed fatal pneumonitis, myocarditis, meningo-encephalitis, and polymyositis. [1]

Tachyzoites disseminate to the brain and the skeletal muscles, and after the onset of the host immune system, they convert into bradyzoite cysts, initiating the chronic form of the disease. To enter the CNS, three mechanisms have been proposed: the "Trojan horse" mechanism, through which the parasite highjacks an immune cell to enter, the paracellular crossing mechanism, and the transcellular crossing mechanism. [9]

Congenital Toxoplasmosis

In sero-negative pregnant women, primary infection with *T. gondii* occurs following the placental transmission of the parasite to the fetus. The degree of severity of congenital toxoplasmosis is inversely related to the gestational trimester at which the infection is acquired. [10]

Although the placenta represents a major forefront that inhibits tachyzoites' transmission in the beginning of gestation, this ability decreases gradually throughout the pregnancy, allowing the tachyzoites to move between cells and infect the fetus. [1]

It is estimated that about 25% of *T. gondii* transmission takes place in the first trimester, whereas 54% and 65% of transmission occur in the second and third trimesters, respectively. Infection of the fetus during the first trimester often leads to abortion, stillbirth, or a child born with severe abnormalities of the brain and eyes, such as hydrocephalus, intracranial calcifications, deafness, mental retardation, seizures, retinochoroiditis, and even blindness. Transmission to the fetus in the second or third trimester is less likely to cause such severe clinical manifestations, but may result in subclinical disease, which may lead to retinochoroiditis or learning difficulties after birth. [11]

It is worth noting that the percentage of acquiring toxoplasmosis during pregnancy varies according to regions and prevalence ,and re-infection with atypical *T. gondii* genotypes was reported even in sero-positive pregnant women , and resulted in a more severe congenital toxoplasmosis. [12]

Ocular Toxoplasmosis

T. gondii is one of the primary causes of infectious uveitis worldwide, typically presenting with retinochoroiditi. Ocular toxoplasmosis mostly occurs after an acquired congenital toxoplasmosis. Yet, some studies reveal postnatal acquired infections leading to this manifestation. Clinical features of ocular toxoplasmosis depend on the anatomical location of the lesion. **(13)**

Typically, retinochoroiditis is the most predominant indication of active intraocular inflammation. It presents with posterior uveitis, vitritis, focal necrotizing granulomatous retinitis, and reactive granulomatous choroiditis.

The rupture of intra-retinal cysts may lead to the reactivation of ocular toxoplasmosis, triggering a rapid localized immune reaction involving mostly Interleukin-17A. **(14)**

Chronic Toxoplasmosis

T. gondii can be classified as a primarily neurotropic pathogen, having a higher affinity for the central nervous system over other organs. **(14)**

To reach the brain parenchyma from the cerebral blood circulation, different strains of T. gondii cross the brain endothelium to the capillary bedding through either hijacking leukocytes or as free parasites. Once the blood brain barrier is crossed, the host immune response, among other factors including intracellular neuronal homeostasis, is triggered, and consequently, T. gondii tachyzoites switch to forming bradyzoite cysts, which are the hallmark of the chronic phase of the infection. These intraneuronal cysts are controlled but not eliminated by the immune system. **(15)**

IV. TOXOPLASMOSIS IN IMMUNOCOMPROMISED PATIENTS

The host immune response plays a key role in the control of parasite replication and maintenance of tissue cysts. With the growing number of individuals receiving immune-suppressive therapies, clinicians are aware of the potential occurrence of *Toxoplasma* encephalitis, not only during the reactivation of latent infection, but also as a primary infection. **(16)**

Indeed, despite the availability of prophylactic and treatment options, the reactivation of chronic toxoplasmosis still occurs and can become life threatening.**(3)**

In immunocompromised patients, the reactivation of chronic toxoplasmosis is due to various factors impairing the protective cellular immune response such as HIV infection, immunosuppressive therapies administered in the context of hematopoietic stem cell transplantation, solid organ transplant, or chemotherapy against cancer. In HIV patients, toxoplasmic encephalitis is the predominant manifestation of the disease, while pulmonary or disseminated toxoplasmosis is more characteristic of transplant patients. **(1)**

These patients present with neurologic symptoms, most frequently diffuse encephalopathy, meningoencephalitis, cerebral mass lesions, headaches, confusion, poor coordination, and seizures. Moreover, in patients with HIV, an association between CD4 counts and the prevalence of *T. gondii*-related neurologic symptoms was reported. In that sense, the reactivation of chronic toxoplasmosis becomes a concern when the CD4 count falls below 200 cells/microliter **(17)**

This reactivation is due to the consequential decrease in IFN-γ and cytokine production, leading to impaired cytotoxic T-lymphocyte activity. Recent data revealed that HIV patients who presented with symptoms of fever and dizziness as part of their *Toxoplasma* encephalitis prodrome sought medical care quicker than those who did not present with these symptoms, leading to the swift administration of treatment, thus reducing mortality. The reactivation of chronic toxoplasmosis was also reported following chemotherapy administration. Indeed, several cases of reactivation of cerebral toxoplasmosis following rituximab therapy were described. The reactivation of toxoplasmosis is also a concern in solid organ transplant recipients, either as a manifestation derived from an infected donor, a reactivation of chronic toxoplasmosis in the recipient, or to a much lesser extent, a primary acquired infection following transplantation. The highest risk of toxoplasmosis was described in orthotopic heart transplant recipients due to the propensity of bradyzoite cysts to form in striated muscles. This enhanced the screening for *T. gondii* in these patients prior to transplantation. **(18)**

A retrospective review of solid organ transplant and hematopoietic stem cell transplant recipients with toxoplasmosis between 2002 and 2018 at two large US academic transplant centers was recently conducted. The median time from transplant to toxoplasmosis diagnosis was longer for solid organ transplants than for hematopoietic stem cell transplants, and clinical manifestations were encephalitis (65%), respiratory failure (40%), renal failure (40%), and distributive shock (40%). The cohort 30-day mortality was 45%, and the 90-day mortality was 55% of the cohort. **(19)**

V. TOXOPLASMA GONDII-ASSOCIATED DISEASES

In healthy individuals, chronic toxoplasmosis was regarded as clinically asymptomatic. However, an increasing number of associations are being made between various medical conditions and *T. gondii* infections. **(20)**

These comprise primary neuropathies, behavioral and psychiatric disorders, and different types of cancer. **(21)**

Stallion Journal for Multidisciplinary Associated Research Studies
ISSN (Online): 2583-3340
Volume-3 Issue-4 || August 2024 || PP. 1-10 https://doi.org/10.55544/sjmars.3.4.1

✓ ***Toxoplasma gondii and Primary Neuropathies***

Associations between T. gondii infection and primary neurologic diseases such as multiple sclerosis, epilepsy, and Parkinson's and Alzheimer's disease remain limited to correlation, controversial studies, and lack a direct molecular proof **(Figure 2).**

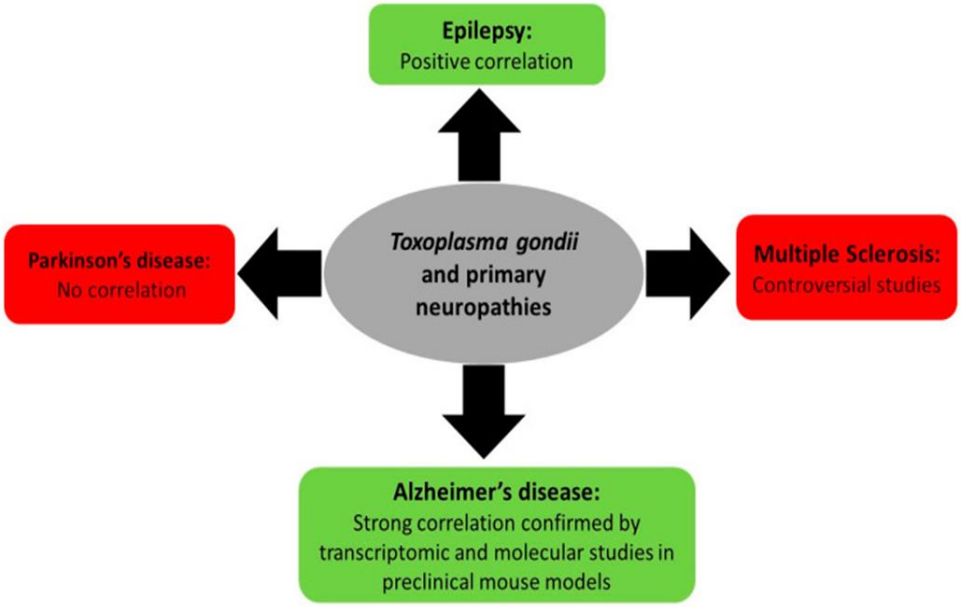

Figure 2: Summary of Toxoplasma gondii-associated primary neuropathy diseases and their outcome.

✓ ***Toxoplasmosis and Multiple Sclerosis***

Multiple sclerosis (MS) is a chronic autoimmune inflammatory multifactorial disease that affects the nervous system, leading to cognitive, neurological, and physical disabilities. Four out of five studies showed a negative association between T. gondii and MS and only one unveiled a positive association. [(21)]

✓ ***Toxoplasmosis and Epilepsy***

Cryptogenic epilepsies represent 20% of epilepsy syndromes with an unknown etiology that are usually due to a suspected underlying brain disease. A study investigated the correlation between cryptogenic epilepsy and toxoplasmosis by choosing a subpopulation of cryptogenic epilepsy patients and testing for T. gondii antibodies. The results were compared with known-cause epilepsy patients and with controls. Cryptogenic epilepsy patients recorded a significant and greater percentage of anti T. gondii IgG antibodies (54%) as compared to 22% in known-cause epilepsy patients and 18% in non-epileptic healthy controls. [(22)]

Similarly, ELISA performed on 22 cryptogenic epilepsy patients revealed that 75% of these patients had greater T. gondii antibody titers than those recorded among the controls. [(23)]

Finally, a meta-analysis study highlighted the increased odds ratio to 1.72 for Toxoplasmosis infection among patients with epilepsy and a significant association between both cryptogenic and active convulsive epilepsy with T. gondii infection. [(24)] These studies favor a potential association between T. gondii and epilepsy.

✓ ***Toxoplasmosis and Parkinson's and Alzheimer's Neuropathies***

Antibodies against Toxoplasma gondii infection were investigated in Parkinson's and Alzheimer's patients. No significant association was reported between toxoplasmosis and Parkinson's disease [(25)]

VI. TOXOPLASMA GONDII, PSYCHIATRIC AND BEHAVIORAL DISORDERS

One of the mechanisms ensuring *T. gondii* expansion throughout its life cycle involves behavioral changes between intermediate and final hosts. Indeed, behavioral peculiarities were reported in infected rodents, which exhibit attenuated aversion and fear and do not flee cats' urine odor. [(26)]

In humans, an increasing body of literature indicates that chronic toxoplasmosis is associated with aberrant host behavior and influences the progression of psychiatric disorders, such as schizophrenia, bipolar disorder, and obsessive compulsive disorder [(27)] **(Figure 3).**

This is partly due to altered dopamine levels following *T. gondii* infection [(28)]

The mechanisms underpinning these changes are still vague and complex, and seem to involve the immune response, hormonal changes, genetic and epigenetic factors as well as structural effects on the infected area of the brain.

Stallion Journal for Multidisciplinary Associated Research Studies
ISSN (Online): 2583-3340
Volume-3 Issue-4 || August 2024 || PP. 1-10 https://doi.org/10.55544/sjmars.3.4.1

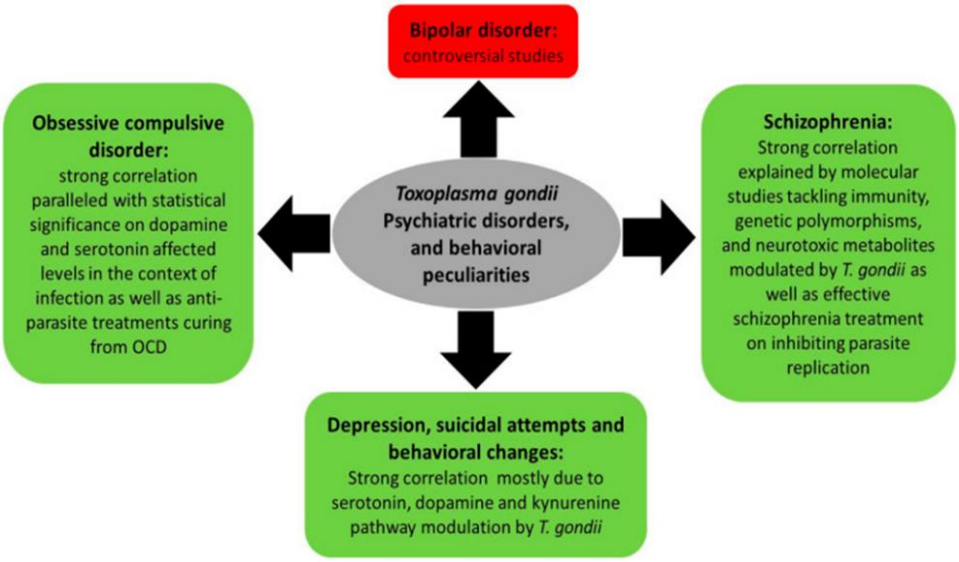

Figure 3: Summary of Toxoplasma gondii-associated psychiatric and behavioral disorders and the molecular status dictating these associations.

- ***Toxoplasmosis, Depression, and Behavioral Changes***

Depression, a mood disorder is characterized by altered levels of serotonin and dopamine. Decreased levels of serotonin are at the cornerstone of depression. Tryptophan, serotonin's precursor, is essential for Toxoplasma growth. [(29)] T. gondii infection triggers inflammatory molecules such as IL-2, IFN-γ, and TNF-α, which consequently upregulate IDO and TDO, hence shunting tryptophan into a degradation pathway. Tryptophan is degraded into kynurenine by indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO). The depletion of tryptophan promotes the onset of depression [(30)]

- ***Toxoplasmosis and Schizophrenia***

Schizophrenia is a psychiatric disorder encompassing varying degrees of delusions, disorganized thoughts, hallucinations that are mainly auditory, disorganized behaviors, and negative symptoms such as having a blunted affect. Difficulties in social interactions, emotions, and overall functionality are also noticed. Different studies associated T. gondii infections with schizophrenia. It was indeed reported that chronic toxoplasmosis associated with schizophrenia is characterized by a significant reduction in gray matter; a finding not seen in the control groups [(31)]

- ***Toxoplasmosis and Bipolar Disorder***

Bipolar disorder (BD), known as manic depression, is a psychiatric disorder in which the patient suffers from rapid or sudden mood changes fluctuating between extreme euphoria to extreme sadness and depression. The etiology of BD is complex and encompasses brain and peripheral chronic inflammation, immune dysfunction, genetic inheritance, and environmental risk factors. Different correlation studies were conducted between toxoplasmosis and bipolar disorders and were contentious. While some studies revealed an increased prevalence of T. gondii in these individuals, other studies showed no correlation.

In BD patients infected with T. gondii, increased levels of kynurenine and kynurenic acid are documented, which correlates with fluctuating levels of dopamine and glutamate as well as the production of neurotoxic factors [(32)]

- ***Toxoplasmosis and Obsessive Compulsive Disorder***

According to the World Health Organization, obsessive compulsive disorder (OCD) is a mental disorder ranked among the top ten life-quality-reducing mental disorders. People with OCD cannot control their thoughts and obsessively repeat activities such as washing hands, checking doors, among others. A meta-analysis pooling 11 studies (9873 participants, including 389 OCD patients) showed a strong correlation between the prevalence of toxoplasmosis and OCD, with a statistically significant odds ratio of correlation with increased dopamine levels.

Other studies suggest that toxoplasmosis leads to changes in hypothalamic–pituitary–adrenal gland axis activity and hormonal disorders including serotonin, which can also lead to OCD. The treatment of two children diagnosed with OCD and seropositive for T. gondii with anti-protozoan medication resulted in both decreased levels of antibodies and a total cure from OCD [(33)]

Stallion Journal for Multidisciplinary Associated Research Studies
ISSN (Online): 2583-3340
Volume-3 Issue-4 || August 2024 || PP. 1-10 https://doi.org/10.55544/sjmars.3.4.1

VII. TREATMENT

Sulfonamides, clindamycin, spiramycin, and pyrimethamine are effective against *T. gondii* infection. The drug combinations sulfadiazine/pyrimethamine and sulfadoxine/pyrimethamine have a synergistic anti-Toxoplasma effect. The recommended prophylaxis against toxoplasmosis in immunocompromised patients is through administration of co-trimoxazole (trimethoprim plus sulfamethoxazole or TMP-SMX). Treatment regime entails one double strength or two single strength daily doses for life or until CD4 counts exceed 200 cells/mm^3 on highly active antiretroviral therapy. **(34)**

VIII. DIAGNOSIS

An accurate diagnosis of toxoplasmosis constitutes an important measure for the control of the disease, particularly during pregnancy. It may also avoid serious economic losses in the sheep and goat industry. *Toxoplasma gondii* infection can be diagnosed using direct or indirect techniques **(2)** Indirect serological techniques serological diagnosis entails detection of specific anti-*Toxoplasma* immunoglobulins, i.e., IgM, IgG, or IgA. **(35)**

This is accomplished through application of immunology-based techniques, e.g., enzyme-linked immunosorbent assays (ELISA), Sabin-Feldman dye test, immunofluorescent assay (IFA), or modified agglutination test (MAT).

Direct diagnosis entails the detection of whole or fractions of parasite, e.g., nucleic acids or proteins by polymerase chain reaction (PCR), loop-mediated isothermal amplification (LAMP), hybridisation, and histology. Whereas indirect serological methods are widely used in immunocompetent patients, definitive diagnosis in immunocompromised people is mostly undertaken by direct detection of the parasite. To discriminate chronic from reactivated infection, IgG avidity can also be determined with VIDAS instrument (bioMerieux, France). Common *T. gondii* targets for direct diagnosis are the repetitive 529 base pairs fragment repeated 200–300 times in the parasite genome and B1 gene **(36)**

IX. TOXOPLASMOSIS AND PROPHYLAXIS: AVAILABLE AND POTENTIAL VACCINE STRATEGIES

Due to the burdensome effects of toxoplasmosis and the failure and/or adverse effects of the currently used therapeutic approaches, several attempts were made to develop vaccines against T. gondii. In 1995, the first commercial vaccine for toxoplasmosis, Ovilis Toxovax, was developed. It consisted of an injectable suspension of attenuated parasites of the strain S48, originally isolated from a case of ovine abortion in New Zealand. Following approximately 3000 passages in mice, this strain lost its ability to differentiate into tissue cysts in mice and into oocysts in cats. This live vaccine was used to prevent toxoplasmosis-induced abortions in sheep, but did not reach human trials due to the high capacity of the parasite to revert back to its pathogenic features. Other vaccine candidates were tested, including apical complex proteins from T. gondii (rhoptries, micronemes, and dense granules), multi-antigen vaccines, and other adjuvants. However, these attempts failed to yield proper protection against toxoplasmosis in humans. In addition, some classes of antigens were proposed to be potential vaccine candidates. These include the Recombinant Surface Antigen-1 (SAG-1), which is a GPI-anchored and highly immunogenic surface marker of the tachyzoite stage of T. gondii and which may protect against acute toxoplasmosis and thus brain cyst formation. Recombinant GRA4 and ROP2 given with Alum adjuvant were also proposed and provided protection against brain cyst formation in C57BL/6 mice. A mixture of SAG1, GRA1, and Merozoite Antigen-1 (MAG1), given with Freund's Complete Adjuvant, reduced brain cyst burden by 90% in BALB/c mice. A mixture of GERBU, an adjuvant based on cationic lipid solid nanoparticles and Nacetylglucosaminyl- N-acetylmuramyl-l-alanyl-d-isoglutamine, a glycopeptide derived from Lactobacillus bulgaricus cell walls, with GRA7 and a MIC2-MIC3-SAG1 chimeric protein provided an 80% reduction in brain cysts in outbred SWISS mice following challenge with T. gondii 76K. Finally, the double knock-out of MIC1-MIC3 genes markedly impaired virulence and conferred protection from T. gondii. **(37)**

X. CONCLUSION

Despite its prevalence, toxoplasmosis remains a neglected disease. Increased statistical correlations between toxoplasmosis and neurologic, psychiatric, and cancer disorders have been unveiled. Addressing the molecular players underlying these associations is paramount in creating avenues for new treatment modalities, especially in light of the absence of a gold standard treatment and a human vaccine against toxoplasmosis. To reach this aim, establishing appropriate animal models of primary neuropathies and behavioral disorders is a must. Indeed, some available pre-clinical models recapitulate the features of some of these diseases, but the absence of the appropriate model remains a challenge for most of them. The recent advances in high-throughput sequencing and proteomics techniques should help in apprehending the correct molecular markers and biomarkers between the parasite and its associated diseases. In addition, the ease of genetic manipulation using multiple tools, including the CRISPR-cas9 targeted disruption or knock-in for genes in *T.*

gondii, will help increase our understanding of the molecular players to confirm the positive correlations between toxoplasmosis and primary neuropathies/associated diseases and solve the enigma of the available controversial studies. Finally, clinicians should increase their awareness of reactivation in immunocompromised patients, an area of interest in which quick molecular diagnostic tests are still lacking.

REFERENCES

[1] Robert-Gangneux F., Darde M. L. (2012). Epidemiology of and diagnostic strategies for toxoplasmosis. *Clin. Microbiol. Rev.* 25, 264–296. 10.1128/CMR.05013-11 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[2] Montoya J. G., Liesenfeld O. (2004). Toxoplasmosis. *Lancet* 363, 1965–1976. 10.1016/S0140-6736(04)16412-X [PubMed] [CrossRef] [Google Scholar]

[3] Meireles L. R., Ekman C. C., de Andrade H. F., Jr., Luna E. J. (2015). Human toxoplasmosis outbreaks and the agent infecting form. Findings from a systematic review. *Rev. Inst. Med. Trop. Sao. Paulo.* 57, 369–376. 10.1590/S0036-46652015000500001 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[4] Chehrazi-Raffle A., Luu M., Yu Z., Liou F., Kittleson M., Hamilton M., et al. . (2015). *Toxoplasma gondii* serology and outcomes after heart transplantation: contention in the literature. *Transplant. Proc.* 47, 1949–1953. 10.1016/j.transproceed.2015.06.022 [PubMed] [CrossRef] [Google Scholar]

[5] Chehrazi-Raffle A., Luu M., Yu Z., Liou F., Kittleson M., Hamilton M., et al. . (2015). *Toxoplasma gondii* serology and outcomes after heart transplantation: contention in the literature. *Transplant. Proc.* 47, 1949–1953. 10.1016/j.transproceed.2015.06.022 [PubMed] [CrossRef] [Google Scholar]

[6] Gajurel K., Dhakal R., Montoya J. G. (2015). *Toxoplasma* prophylaxis in haematopoietic cell transplant recipients: a review of the literature and recommendations. *Curr. Opin. Infect. Dis.* 28, 283–292. 10.1097/QCO.0000000000000169 [PubMed] [CrossRef] [Google Scholar]

[7] Wei Cong, Guo-Hua Liu, Qing-Feng Meng, et al. Toxoplasma gondii infection in cancer patients: prevalence, risk factors, genotypes and association with clinical diagnosis. 2015 Apr 10;359(2):307-13. doi: 10.1016/j.canlet.2015.01.036.

[8] Ben-Harari R.R., Connolly M.P. High burden and low awareness of toxoplasmosis in the United States. *Postgrad. Med.* 2019;131:103–108. doi: 10.1080/00325481.2019.1568792. [PubMed] [CrossRef] [Google Scholar]

[9] Mendez O.A., Koshy A.A. *Toxoplasma gondii*: Entry, association, and physiological influence on the central nervous system. *PLoS Pathog.* 2017;13:e1006351. doi: 10.1371/journal.ppat.1006351. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[10] Yamamoto L., Targa L.S., Sumita L.M., Shimokawa P.T., Rodrigues J.C., Kanunfre K.A., Okay T.S. Association of Parasite Load Levels in Amniotic Fluid With Clinical Outcome in Congenital Toxoplasmosis. *Obstet. Gynecol.* 2017;130:335–345. doi: 10.1097/AOG.0000000000002131. [PubMed] [CrossRef] [Google Scholar]

[11] Weiss L.M., Dubey J.P. Toxoplasmosis: A history of clinical observations. *Int. J. Parasitol.* 2009;39:895–901. doi: 10.1016/j.ijpara.2009.02.004. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[12] Delhaes L., Ajzenberg D., Sicot B., Bourgeot P., Dardé M.-U., Dei-Cas E., Houfflin-Debarge V. Severe congenital toxoplasmosis due to a *Toxoplasma gondii* strain with an atypical genotype: Case report and review. *Prenat. Diagn.* 2010;30:902–905. doi: 10.1002/pd.2563. [PubMed] [CrossRef] [Google Scholar]

[13] Delair E., Latkany P., Noble A.G., Rabiah P., McLeod R., Brezin A. Clinical manifestations of ocular toxoplasmosis. *Ocul. Immunol. Inflamm.* 2011;19:91–102. doi: 10.3109/09273948.2011.564068. [PubMed] [CrossRef] [Google Scholar]

[14] Sauer A., Rochet E., Lahmar I., Brunet J., Sabou M., Bourcier T., Candolfi E., Pfaff A.W. The local immune response to intraocular Toxoplasma re-challenge: Less pathology and better parasite control through Treg/Th1/Th2 induction. *Int. J. Parasitol.* 2013;43:721–728. doi: 10.1016/j.ijpara.2013.04.004. [PubMed] [CrossRef] [Google Scholar]

[15] Matta S.K., Rinkenberger N., Dunay I.R., Sibley L.D. *Toxoplasma gondii* infection and its implications within the central nervous system. *Nat. Rev. Microbiol.* 2021;19:467 480. doi: 10.1038/s41579-021-00518-7. [PubMed] [CrossRef] [Google Scholar]

[16] Gharamti A.A., Rao A., Pecen P.E., Henao-Martínez A.F., Franco-Paredes C., Montoya J.G. Acute Toxoplasma Dissemination With Encephalitis in the Era of Biological Therapies. *Open Forum. Infect. Dis.* 2018;5:256–259. doi: 10.1093/ofid/ofy259. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[17] Bannoura S., El Hajj R., Khalifeh I., El Hajj H. Acute disseminated encephalomyelitis and reactivation of cerebral toxoplasmosis in a child: Case report. *IDCases.* 2018;13:e00434. doi: 10.1016/j.idcr.2018.e00434. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[18] Rajapakse S., Weeratunga P., Rodrigo C., Lakshitha de Silva N., Fernando S.D. Prophylaxis of human toxoplasmosis: A systematic review. *Pathog. Glob. Health.* 2017;111:333–342. doi: 10.1080/20477724.2017.1370528. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[19] La Hoz R.M., Morris M.I. Infectious Diseases Community of Practice of the American Society of, Tissue and blood protozoa including toxoplasmosis, Chagas disease, leishmaniasis, Babesia, Acanthamoeba, Balamuthia, and Naegleria in solid organ transplant recipients-Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transpl.* 2019;33:e13546. [PubMed] [Google Scholar]

[20] Adekunle R.O., Sherman A., Spicer J.O., Messina J.A., Steinbrink J.M., Sexton M.E., Lyon G.M., Mehta A.K., Phadke V.K., Woodworth M.H. Clinical characteristics and outcomes of toxoplasmosis among transplant recipients at two US academic medical centers. *Transpl. Infect Dis.* 2021;23:e13636. doi: 10.1111/tid.13636. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[21] Madireddy S., Rivas Chacon E.D., Mangat R. *Toxoplasmosis, in StatPearls.* StatPearls Publishing; Treasure Island, FL, USA: 2020. [Google Scholar]

[22] Ngo H.M., Zhou Y., Lorenzi H., Wang K., Kim T.K., Zhou Y., El Bissati K., Mui E., Fraczek L., Rajagopala S.V., et al. Toxoplasma Modulates Signature Pathways of Human Epilepsy, Neurodegeneration and Cancer. *Sci. Rep.* 2017;7:11496. doi: 10.1038/s41598-017-10675-6. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[23] Saberi R., Sharif M., Sarvi S., Aghayan S.A., Hosseini S.A., Anvari D., Chegeni T.N., Hosseininejad Z., Daryani A. Is *Toxoplasma gondii* playing a positive role in multiple sclerosis risk? A systematic review and meta-analysis. *J. Neuroimmunol.* 2018;322:57–62. doi: 10.1016/j.jneuroim.2018.06.011. [PubMed] [CrossRef] [Google Scholar]

[24] Yazar S., Arman F., Yalçin S., Demirtaş F., Yaman O., Sahin I. Investigation of probable relationship between *Toxoplasma gondii* and cryptogenic epilepsy. *Seizure.* 2003;12:107–109. doi: 10.1016/S1059-1311(02)00256-X. [PubMed] [CrossRef] [Google Scholar]

[25] Stommel E.W., Seguin R., Thadani V.M., Schwartzman J.D., Gilbert K., Ryan K.A., Tosteson T.D., Kasper L.H. Cryptogenic Epilepsy: An. Infectious Etiology? *Epilepsia.* 2001;42:436–438. doi: 10.1046/j.1528-1157.2001.25500.x. [PubMed] [CrossRef] [Google Scholar]

[26] Sadeghi M., Riahi S.M., Mohammadi M., Saber V., Aghamolaie S., Moghaddam S.A., Aghaei S., Javanian M., Gamble H.R., Rostami A. An updated meta-analysis of the association between *Toxoplasma gondii* infection and risk of epilepsy. *Trans. R. Soc. Trop Med. Hyg.* 2019;113:453–462. doi: 10.1093/trstmh/trz025. [PubMed] [CrossRef] [Google Scholar]

[27] Bayani M., Riahi S.M., Bazrafshan N., Gamble H.R., Rostami A. *Toxoplasma gondii* infection and risk of Parkinson and Alzheimer diseases: A systematic review and meta-analysis on observational studies. *Acta Trop.* 2019;196:165–171. doi: 10.1016/j.actatropica.2019.05.015. [PubMed] [CrossRef] [Google Scholar]

[28] Tong W.H., Pavey C., O'Handley R., Vyas A. Behavioral biology of *Toxoplasma gondii* infection. *Parasit. Vectors.* 2021;14:77. doi: 10.1186/s13071-020-04528-x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[29] Severance E.G., Xiao J., Jones-Brando L., Sabunciyan S., Li Y., Pletnikov M., Prandovszky E., Yolken R. *Toxoplasma gondii*-A Gastrointestinal Pathogen Associated with Human Brain Diseases. *Int. Rev. Neurobiol.* 2016;131:143–163. [PMC free article] [PubMed] [Google Scholar]

[30] Wang Z.T., Harmon S., O'Malley K.L., Sibley D.L. Reassessment of the role of aromatic amino acid hydroxylases and the effect of infection by *Toxoplasma gondii* on host dopamine. *Infect Immun.* 2015;83:1039–1047. doi: 10.1128/IAI.02465-14. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[31] Murakami Y., Hoshi M., Hara A., Takemura M., Arioka Y., Yamamoto Y., Matsunami H., Funato T., Seishima M., Saito K. Inhibition of increased indoleamine 2,3-dioxygenase activity attenuates *Toxoplasma gondii* replication in the lung during acute infection. *Cytokine.* 2012;59:245–251. doi: 10.1016/j.cyto.2012.04.022. [PubMed] [CrossRef] [Google Scholar]

[32] Mahmoud M.E., Fereig R., Nishikawa Y. Involvement of Host Defense Mechanisms against *Toxoplasma gondii* Infection in Anhedonic and Despair-Like Behaviors in Mice. *Infect. Immun.* 2017;85:e00007–e00017. doi: 10.1128/IAI.00007-17. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[33] Webster J.P., McConkey G.A. *Toxoplasma gondii*-altered host behaviour: Clues as to mechanism of action. *Folia. Parasitol. (Praha)* 2010;57:95–104. doi: 10.14411/fp.2010.012. [PubMed] [CrossRef] [Google Scholar]

[34] Akaltun İ., Kara S.S., Kara T. The relationship between *Toxoplasma gondii* IgG antibodies and generalized anxiety disorder and obsessive-compulsive disorder in children and adolescents: A new approach. *Nord. J. Psychiatry.* 2018;72:57–62. doi: 10.1080/08039488.2017.1385850. [PubMed] [CrossRef] [Google Scholar]

[35] M. Vogel, C. Schwarze-Zander, J.-C. Wasmuth, U. Spengler, T. Sauerbruch, and J. K. Rockstroh, "The treatment of patients with HIV," *Deutsches Ärzteblatt International*, vol. 107, no. 28-29, pp. 507–516, 2010.View at: Publisher Site | Google Scholar

[36] Calderaro, S. Peruzzi, G. Piccolo et al., "Laboratory diagnosis of *Toxoplasma gondii* infection," *International Journal of Medical Sciences*, vol. 6, no. 3, pp. 135-136, 2009.View at: Publisher Site | Google Scholar

[37] W. L. Homan, M. Vercammen, J. De Braekeleer, and H. Verschueren, "Identification of 200- to 300-fold repetitive 529 bp DNA fragment in *Toxoplasma gondii*, and its use for diagnostic and quantitative

PCR[1],” *International Journal for Parasitology*, vol. 30, no. 1, pp. 69–75, 2000.View at: Publisher Site | Google Scholar

[38] 188. Lee D.H., Kim A.R., Lee S.H., Quan F.S. Cross-protection induced by *Toxoplasma gondii* virus-like particle vaccine upon intraperitoneal route challenge. *Acta Trop.* 2016;164:77–83. doi: 10.1016/j.actatropica.2016.08.025. [PubMed] [CrossRef] [Google Scholar]