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Warm-blooded animal toxoplasmosis and its connection to COVID-19: A review

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ABSTRACT

Toxoplasmosis is a zoonotic illness that spreads from animals to people. *Toxoplasma gondii*, a protozoan parasite that infects warm-blooded mammals, causes the sickness. Toxoplasmosis is a parasitic infection that causes abortion and death in animals. Cats are the parasite's sole sexual hosts, thus they're the only ones who can get it. Because cats are frequent pets, they are highly likely to come into touch with humans. As a result, the disease poses a risk to human health. The potential danger is influenced by the frequency of oocyst secretion and the level of contamination in the environment. Toxoplasmosis has serious consequences for both animal and human health, hence preventative actions should be taken to reduce the dangers. COVID-19 is affected by such methods as well. Toxoplasmosis is thought to increase immunological and immunosuppressive factors, which increases the chance of SARS-CoV-2 infection and the severity of the resulting COVID-19. Research into *Toxoplasma gondii* intermediate hosts might help understand COVID-19's dynamics and determine if the virus can be transferred from animals to humans. We explore what we know about *Toxoplasma gondii* infection as a human parasitosis and how it may alter the course of SARS-CoV-2 infection in this review study.

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Introduction

Toxoplasma gondii (*T. gondii*), one of the most common parasites on the planet, is thought to infect up to one-third of the world's population (Montoya & Liesenfeld, 2004). This parasite has a complex life cycle that ends in reproduction and oocyst formation in the intestines of definitive hosts, primarily cats. It is also capable of reproducing in a range of intermediary hosts, including nonhuman animals. When a warm-blooded animal eats sporulated oocysts, sporozoites are released in the colon, where they pierce the lining and form tachyzoites (Gibson 2005). The parasite's only stage of activity in the intermediate host is the conversion of proliferative tachyzoites to quiescent encysted bradyzoites, which is controlled by the host's immune response (Djurković-Djaković et al. 2019). *Toxoplasma*'s three phases

(tachyzoites, bradyzoites, and sporozoites) are all infectious to warm-blooded mammals, and they influence how the disease is transmitted and disseminated to additional hosts (Hill & Dubey 2018). The cat, as the definitive host, is the only intermediate host in which *T. gondii* can complete its sexual cycle. Semi-domestic cats and predatory birds that eat sick rodents can spread the disease to humans (Dubey 2010).

Humans have always faced epidemics, which are caused mostly by infectious diseases carried by animals, particularly wildlife (Figure 1). To establish continuing transmission from early spillover incidents, the interaction of intricate systems that are difficult to understand is essential. However, it is commonly accepted that efficient cross-species transmission requires direct or indirect contact between people and animals, as well as their body fluids (an "animal-human interface"). While people and domestic and

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wild animals have coexisted for millennia, anthropogenic factors have exacerbated the animal-human interface in recent decades, increasing our interaction with animals and, as a result, the risk of disease spread (Montoya & Liesenfeld 2004). Latent toxoplasmosis, a lifelong infection caused by the protozoan parasite *T. gondii*, affects around a third of the world's population. Infected persons have a significantly higher frequency of mental and physical health concerns, as well as being more susceptible to the detrimental effects of various illnesses, according to several research conducted over the previous decade (Djurković-Djaković et al. 2019).

Beyond its established role in toxoplasmosis, *T. gondii* has attracted research attention for its potential role in COVID-19 severity. During the COVID-19 pandemic, finding factors that may increase or decrease the likelihood of COVID-19 has become the topic of considerable research. Several studies have reviewed the relationship between SARS-CoV-2, the virus that causes COVID-19, and toxoplasmosis infection. One study suggested that *T. gondii* infections, either directly or indirectly, are related to higher mortality in COVID-19 patients with schizophrenia (Roe 2022). The impact of toxoplasmosis on the chance of developing COVID-19 and the severity of illness was reported by Flegr (2021a). Latent infections, including *T. gondii* infections, could explain the increased mortality rates for several categories of COVID-19 patients, as well as the incidence of severe COVID-19 symptoms and long COVID-19 (Flegr 2021b; Roe 2021a). *T. gondii* may be a contributing factor in these cases because oocytes residing in the host tissues have previously been shown to promote factors that are associated with a high risk of COVID-19 infection (Varikuti et al. 2018; Ghaffari et al. 2021). Further, toxoplasmosis could increase the risk of COVID-19 due to increased lymphocytic PD-1 expression, and thus it should be considered as a potential factor in the severity of COVID-19 (Xiao et al. 2018; Sharaf-El-Deen et al. 2021). Finally, SARS-CoV-2 has been isolated from a variety of samples collected from cats and dogs residing in the same homes as people infected with SARS-CoV-2 (Jankowiak et al. 2020).

However, some studies have not confirmed that *T. gondii* infection is a risk factor for COVID-19. People who are infected with toxoplasmosis are neither informed about a higher risk nor are they prioritized in vaccination programs. There are no direct causal relationships proved to exist between toxoplasmosis and susceptibility to COVID-19 (Jankowiak et al. 2020; Calvet et al. 2021). Nevertheless, it is recognized that pathogen infections that are latent may induce immune cell dysfunctions, such as T-cell exhaustion. In this situation, the simultaneous presence of multiple pathogens can induce T-cell exhaustion that is known as polyspecific T-cell exhaustion Roe (2021b).

2. Diversity and determinants of *T. gondii* pathogenicity

Some toxoplasma groups are widely distributed across continents, whereas others are successful clonal lineages that are limited to a specific geographical region (Robert-Gangneux & Dardé 2012). Previously described lineages (types I, II, and III) were considered to represent the major groups, which have low genetic diversity. However, as data accumulated, it became apparent that these lineages are most common in North America and Europe, with more types occurring in other parts of the world (Mercier et al. 2010). Overall, 12 groups have been described, including an additional fourth lineage in North America (Khan et al. 2011). This diversity in toxoplasma represents a public health hazard that requires further consideration (Galal et al. 2019). Based on a strain's pathogenicity, *T. gondii* is usually classified as either virulent or avirulent (Ferreira et al. 2018). When environmental and fecal samples are tested, polymerase chain reaction and amplicon sequencing are used to confirm identification (Robertson et al. 2019).

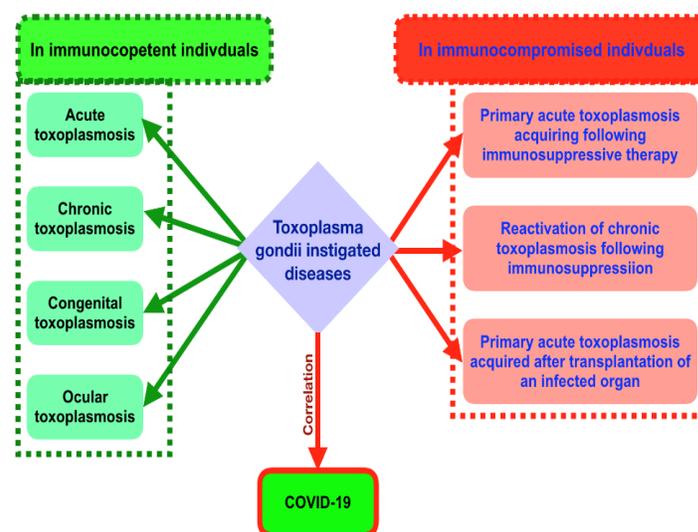


Fig 1. *Toxoplasma gondii* instigated diseases. Here, the list of diseases for immunocompetent and immunocompromised individuals were shown which are directly associated with *T. gondii*.

The virulence of *T. gondii* infection is influenced by a number of variables. Some of these elements have to do with the parasite itself, while others have to do with the immune system of the host. In neutralization studies, proteins related with virulence are recognized based on differences between virulent and avirulent strains (Zhou et al. 2017; Barragan & Sibley, 2002). ROP18 (rhoptry-associated serine/threonine kinase) inactivates p47 GTPases de more virulent *T. gondii* strains, facilitating the bursting of parasite-containing vacuoles in infected cells

(Hermanns et al. 2016). Virulence factors, such as penetration-enhancing factor and membrane antigen proteins, are found in virulent strains, but not in avirulent strains (Bhopale 2003). The more virulent type I *T. gondii* has enhanced migratory capacity across cellular barriers (Barragan & Sibley 2002). Five *T. gondii* genomic regions are associated with virulence and are designated as VIR1–5 (Saeij et al. 2006). Some of these regions have been identified as encoding ROP18 (VIR3), while others are still under investigation to identify their potential roles (Blader & Saeij 2009). Healthy people's immune systems can regulate the illness, reducing its impact on their immunological condition. The infection of *T. gondii* is vital for battling the infection because it may destroy other cells directly, aiding defence against released tachyzoites (Gigley et al. 2009; Vouldoukis et al. 2011; Koshy et al. 2012). However, *T. gondii* infection poses a greater risk to immunocompromised individuals and may even cause death.

2.1. Toxoplasmosis in cats

In terms of transmission and dispersion, *T. gondii* is regarded as a very effective pathogen. Depending on the surrounding environmental circumstances, oocysts can live for up to 18 months (Yan et al., 2016 and Shapiro et al., 2019). Cats, being the parasite's primary host, have the capacity to release millions of oocysts into the environment. At any given moment, about 1% of cats shed oocysts, resulting in 55 million cysts every day or 3–810 million oocysts per cat infection (Torrey & Yolken 2013; Ramakrishnan et al. 2019). *T. gondii* oocysts may be more likely to survive and grow in these settings since cat infections are more common in warm, moist, and low-altitude locations. (Hatam-Nahavandi et al. 2021). Cats are the most common cause of infection in animals. Ingestion of bradyzoites contained within the cysts of uncooked or undercooked meat from chronically infected animals is a second source of horizontal transmission to humans, and it is also the route of infection for the final (feline) host (Stelzer et al. 2019). Finally, vertical transmission may occur when tachyzoites cross the placenta, infecting the developing fetus (Blader et al. 2015). Stray cats have been reported to have significant seroprevalence, which is presumably related to having more opportunity to come into contact with contaminated sources outdoors (Hatam-Nahavandi et al. 2021). Wild animals such as wild boars or foxes also become infected as they feed on infected animals (Mancianti et al. 2020). Some studies have shown that cockroaches and flies transmit the infection by carrying oocysts from cat feces to uncovered food (Torrey & Yolken 2013).

2.2. Toxoplasmosis in Dogs

Dogs are thought to spread toxoplasmosis infection and contribute to the mechanical transmission of the parasite (Tenter et al., 2001; Torrey and Yolken, 2013 and Yang et al., 2013). Dogs might also contribute to the prevalence of infection by scattering oocysts in the environment after ingesting them through shedding. However, the parasite cannot replicate in dogs (Rengifo-Herrera et al. 2017). Dubey et al. (2007) reported 16.8% seroprevalence in unwanted dogs in Bogota, Columbia. Domestic dogs from Minas Gerais and Mato Grosso (Pantanal) in Brazil were found to have seroprevalence of 40.90% and 43.1%, respectively (Brandão et al. 2006 ; Rodrigues et al. 2016).

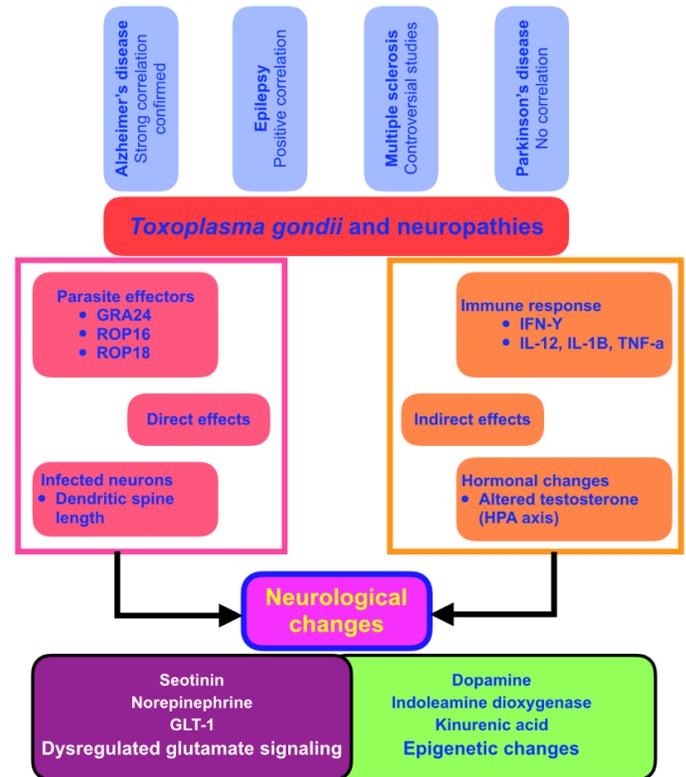


Fig 2. *T. gondii* and neuropathies. It shows the effect of *T. gondii* in neurological system and the afterward changes.

2.3. Toxoplasmosis in domestic animals

Toxoplasmosis has been seen in domestic animals, particularly those that provide food. *T. gondii* was found in 7 out of 2094 pork samples in one investigation, but none in 2094 beef or chicken samples (Dubey et al. 2005). *T. gondii* is more common in reared pigs and poultry than in cattle, owing to outside contact with potentially infected rodents and oocyst contamination of feed, water, and the environment (Guo et al. 2015). Horse meat might also be a cause of food-borne infection in humans. In France, toxoplasmosis has been epidemiologically related to eating horse meat imported from Canada and Brazil (Pomares et al. 2011). In addition, tachyzoites have been identified in

the milk of several intermediate hosts, such as camels (Dubey 2010; Saad et al. 2018). One study of 227 Saudi Arabian camels showed that 16% were serologically positive for toxoplasmosis (Hussein et al. 1988).

2.4. Toxoplasmosis in wild animals

Wild species, such as sea otters, have been found to be infected with *T. gondii*, suggesting that water systems can be contaminated with *T. gondii* oocysts brought into the environment from land locations (Conrad et al., 2005). *T. gondii* was not expected to be found in marine animals; however, many fish-eating animals have been found to be infected with the parasite (Dubey et al. 2003; Conrad et al., 2005). In addition, birds can also develop toxoplasmosis, as shown by the DNA of *T. gondii* having been found in wild birds tested in the Izmir and Manisa regions of Turkey (Karakavuk et al. 2018). Sexual transmission of toxoplasmosis has been reported in various animal species. Dass et al. (2022) and Lopes et al. (2013) respectively observed that female rats and sheep became infected after mating with toxoplasmosis-infected males, and their offspring were later found to be infected as well. Female goats were also reported to be infected after mating with infected males in a study by Santana et al. (2013). One study showed that artificial insemination of female dogs, rabbits, and sheep with semen obtained from infected males led to infection in most cases (Arantes et al. 2009; de Moraes et al. 2010; Liu et al. 2012). *T. gondii* has also been detected in the reproductive organs and semen of a variety of animal species (Moura et al. 2007; Scarpelli et al. 2009; Santana et al. 2013).

Another risk factor for transmission is the variation in temperature and humidity because the environment strongly influences the epidemiology of toxoplasmosis (Tenter et al. 2001; Gebremedhin et al. 2013). Toxoplasmosis prevalence is also influenced by herd size and the type of farm management used. Smaller herds, for example, have a higher risk factor, probably because to more cat contacts and frequent grazing activity. Furthermore, the absence of zoo-hygiene procedures (such as feeding or cleaning) may affect the transmission of oocysts shed by cats (Klun et al. 2006). Experimentally infected sheep did not exhibit any clinical signs of infection (fever, abortion, stillbirth) when tested. *T. gondii* can also be sexually transmitted through semen (de Moraes et al. 2010; Lopes et al. 2013), with infected rams becoming infertile (Savvulidi et al. 2018).

3. COVID-19 and Toxoplasmosis

Individuals with diseases such as toxoplasmosis may be more susceptible to COVID-19. Increased lymphocyte PD-1 expression is linked to toxoplasma, which is thought to be a possible COVID-19 severity factor (Sharaf-El-Deen et al. 2021; Roe, 2021b). Research has shown an impact of latent

toxoplasmosis on mental and physical health (Torrey & Yolken 2013). An indirect relationship was initially uncovered, in which psychological symptoms connected to chronic stress were shown to explain the majority of previously documented differences in personality and behaviour between infected and non-infected people (Lindová et al. 2010). A correlation between *T. gondii* infection and latent toxoplasmosis in COVID-19 patients has been observed, and due to a high spread rate of latent toxoplasmosis in humans, reactivation of latent infection should be considered following immunosuppressive therapy in COVID-19 patients (Abdoli et al. 2021). The strongest links between latent toxoplasmosis and coronary artery disease, foetal discomfort, and birth abnormalities exist. Toxoplasmosis has been linked to a variety of significant problems, including persistent weariness and accelerated ageing, according to another research (Havlíček et al. 2001). People infected with *T. gondii* have been observed to have more severe symptoms, including COVID-19. Toxoplasmosis-infected males had increased testosterone levels, according to several research, including clinical trials and in vivo animal studies (Flegr et al. 2008; Tan & Vyas 2016). Since it is a newly identified illness, COVID-19 likely appeared after Czech volunteers were diagnosed with toxoplasmosis, it was found that COVID-19 has an association with toxoplasmosis (Flegr 2021a).

A proportion of patients with COVID-19 have experienced neurological and psychological symptoms, including fatigue, shortness of breath, and impaired senses of smell and taste, that have persisted for months beyond the initial illness (Figure 2) (Varikuti et al. 2018; Roe, 2021a; Ghaffari et al. 2021). Almost all of the symptoms of what is now known as protracted COVID-19 are similar to those seen in people who have a *T. gondii* infection that is current or reactivated (Vidal 2019). Shortness of breath, fevers, seizures, headaches, visual changes, cognitive impairment, mental disorientation, incoordination, involuntary movements, pneumonia, and a variety of cranial nerve palsies are all signs of toxoplasmosis (Vidal 2019). Inflammatory alterations, neurotransmitter disruptions, and immunological dysfunctions, such as CD8 T cell depletion, have all been linked to *T. gondii* infection. Infections like this have been linked to the development of schizophrenia in the past. Patients with positive test findings for *T. gondii* brain infection had a higher risk of SARS-CoV-2-induced neuro-inflammation and CD8 T-cell exhaustion, leading to increased SARS-CoV-2 mortality, according to studies on SARS-CoV-2 infections in schizophrenia patients. Reactivation/infection with *T. gondii* might explain why patients have such a wide range of symptoms during and after SARS-CoV-2 infections. (Roe 2021b). Toxoplasma can latently infect hosts, and part of the parasite's biological adaptability is the ability to survive being targeted by a

host's immune system (Flegr 2021a). In another study, the virus was inhibited by the parasite, and its spread decreased, further, normal concentrations of Zn in the context of toxoplasmosis help to diminish the sequelae of COVID-19 (Hamad & Garedaghi 2021).

4. Treatment of Toxoplasmosis in Animals

Several drugs are used globally to treat toxoplasmosis. The most frequently used drugs are sulfadiazine (15–25mg/kg) and pyrimethamine (0.44mg/kg) combined with folinic acid to prevent the suppression of bone marrow production by pyrimethamine. These drugs are effective at treating the acute stage of the disease when the parasite is actively multiplying. However, they cannot eradicate the infection. Other drugs that are used include azithromycin, clarithromycin, atovaquone, and dapsone, and these may be paired with either trimethoprim-sulfamethoxazole or pyrimethamine and folinic acid. These other drugs have less toxicity, but are also less effective (Arora and Arora, 2018). Clindamycin is often used when animals cannot tolerate sulfonamides, while atovaquone is used when sulfonamides or clindamycin cannot be used. Clindamycin is typically used to treat dogs and cats, at 10–40mg/kg and 25–50mg/kg, respectively, for 14–21 days.

Diaminodiphenylsulfone and spiramycin are also prescribed to treat toxoplasmosis in difficult infections (Halonen and Weiss, 2013). Spiramycin is used to treat newly acquired toxoplasmosis in pregnant hosts because it concentrates in the placental tissue, preventing the transmission of the parasite (Arora & Arora, 2018; Konstantinovic et al. 2019). However, spiramycin is not effective at treating established fetal infections, because it hardly passes the placental barrier (Robert-Gangneux & Dardé 2012).

In congenital toxoplasmosis, treatment depends on the point of introduction (i.e., whether it is prenatal or postnatal). Prenatal treatments are typically aimed at preventing materno-fetal transmission or reducing potential damage to the fetus. In comparison, postnatal treatment aims to ease clinical manifestations or prevent the long-term presence of sequelae in the infected neonate (Konstantinovic et al. 2019). Postnatal treatment is usually started as soon as the congenital infection is diagnostically confirmed. The primary aim of this approach is to reduce or eliminate clinical manifestations at birth and to prevent long-term sequelae or clinical relapses. Prenatal diagnosis cannot be performed before the 14th week of gestation; spiramycin treatment is typically used during the first trimester of pregnancy (Konstantinovic et al. 2019; Guegan et al. 2021). Most individuals who experience the early symptoms of COVID-19, such as fever and malaise, but are otherwise healthy may keep reservoirs of SARS-CoV-2 in their body tissue.

5. Prevention

Despite the high incidence of the *T. gondii* parasite in the human population, the progress of vaccine development is noticeably slow because of (1) the relatively infrequent risk to humans and (2) complications in developing a balanced, safe, and efficacious vaccine. Currently, only one vaccine has been produced to protect against *T. gondii* infection, and it is used in sheep (Gibson 2005). This live attenuated vaccine requires passing *T. gondii* tachyzoites 3000 times through mice. It is essential to develop *T. gondii* vaccines for cats and for animals whose meat is consumed by humans to reduce the incidence and transmission of the parasite. However, few antigen candidates are known and they only elicit partial protective immunity, making this target a major challenge (Zhang et al. 2013). In addition, there is a lack of detailed understanding of the cell invasion mechanisms of the parasite and correlates of protection against infection (Liu et al. 2012). Scientists from various disciplines must cooperate to help improve the vaccine development process for toxoplasmosis. The existing treatment options for the major *T. gondii* disease entities have changed little in decades, with no new chemotherapeutic drugs available (Konstantinovic et al. 2019; Guegan et al. 2021).

6. Conclusion

Studies show that individuals infected with *T. gondii* have a greater burden of disease. The present research shows that *T. gondii* infection is a risk factor for a more severe course of COVID-19 following SARS-CoV-2 infection. Long COVID-19 symptom clusters may provide new ideas on the biological factors contributing to the varied clinical courses experienced by individuals after SARS-CoV-2 infection. In such cases, the factor of latent toxoplasmosis appears to have a greater impact on the hazards of COVID-19 than most other known variables. Many people have varied symptoms of long-COVID-19-related ailments after their SARS-CoV-2 infections cease, possibly because latent *T. gondii* infections are reactivated during the illness. Toxoplasmosis is assumed to affect the likelihood of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and the severity of the resultant COVID-19 by increasing immune and immunosuppressive factors.

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