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TOXOPLASMOSIS IN CATS: A ZOONOTIC THREAT

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ABSTRACT
Toxoplasmosis is a protozoan infection of animals and humans caused by *Toxoplasma gondii*. *T. gondii* is one of the most well studied parasite because of its medical and veterinary importance. *Toxoplasma* is used extensively as a model for cell biology of apicomplexan organisms. It is an obligate intracellular parasite that has a characteristically polarized cell structure and a complex cytoskeltal and organellar arrangements at the epical end, the conoid involved in cell invasion and numerous secretory organelles rhoptries (ROPs), dense granules and micronemes. Cats are the definitive host where the mature parasite divides sexually in intestinal mucosa. Three infectious stages of *T.gondii* are found in all host comprising oocysts, bradyzoites and tachyzoites. Infection of cat occurs after ingestion of any of three life stages. The estimated seroprevalence for *T. gondii* in domestic cats, worldwide is 30-40 percent whereas in india, the overall prevalence of toxoplasmosis in cats varied between 2.2% and 4.8%. *Toxoplasma gondii* attacks most organs with predilection for the reticuloendothelial and nervous system. *T. gondii* may spread locally to mesenteric lymph nodes and to distant organ by blood. *T. gondii* may persist longer in the spinal cord and brain because immunity is not able to penetrate the nervous tissue in comparison to visceral organs. Clinical signs in cats are depression, weakness, incoordination, tremors, circling, paresis and blindness. Pneumonia is the main sign of generalized toxoplasmosis. Acute respiratory distress syndrome and septic shock may occur in febrile cats. Chronic, sublethal toxoplasmosis has also been observed in cats. In cats, clinical toxoplasmosis is more severe in transplacentally infected kittens. Among companion animals, fatal toxoplasmosis may occur in dogs that are immunosuppresed. *T. gondii* infection is widespread among humans in different geographical areas. Human acquire their infections from ingestion of oocyst contaminated soil and water, from tissue cyst, by organ transplantation, blood transfusion, laboratory accidents or congenitally.

KEY WORDS: Toxoplasmosis in cats, *T.gondii*, Obligate intracellular parasite, Zoonotic threat.

INTRODUCTION

The population of domestic cats is growing worldwide, owing to their adaptability to a modern lifestyle. In present time, as cats transitioned from pet to a family member, the provision of their health care has become a cause of worry for the family members. Nowadays, the transmission of the pathogens from the pets to surfaces and rooms accessible to other animals and people that share the same environment has become easier as the pets are provided great freedom when living inside houses. Regardless of the benefits pets provide to people, they also pose potential health hazards (Dabritz & Conrad, 2010). Toxoplasmosis is a protozoan infection of animals and humans caused by *Toxoplasma gondii*. *T. gondii* oocysts are only shed by the felids, thus cat feces are the source of oocysts. The owners are at risk of infection after their pet acquires the primary infection with *T. gondii* and may shed large numbers of oocysts into the household. Livestock at a farm is generally infected by the stray cats or cats that are roaming on farms. The infected livestock that will later be slaughtered for human consumption also poses a threat to the environment, if not properly cooked. However, the oocysts shed by cats are not immediately infectious as they are unsporulated (Tenter, 2009).

Toxoplasma gondii has a high worldwide distribution in human populations as it infects approximately one third of global population (approximately 500 million) and a wide range of other mammalian and avian species. It has a high socio- economic impact in terms of human suffering including the cost of caring for sick mentally retarded and blind children and therefore is a major health problem. It is a major cause of infertility and abortion in livestock, especially among ewes and therefore a significant cause of lost profitability in livestock and agriculture. In immunodeficient patients, including AIDS, it is a major cause of morbidity. *T.gondii* contributes to be an important emerging human disease especially of pregnant woman (Furtado *et al*., 2011).

ETIOLOGY

Toxoplasma gondii belongs to the Kingdom Animalia, Phylum Apicomplexa, Class Protozoa, Subclass Coccidian, Order Eucoccidia, Family Sarcocystidae and Genus *Toxoplasma*. It is an obligate intracellular protozoan parasite that has a characteristically polarized cell structure and a complex cytoskeletal and organellar arrangement at the apical end, the conoid, involved in cell invasion and numerous secretory organelles rhoptries (ROPs), dense granules, and micronemes (Tilahun, 2015). It was previously considered that *T. gondii* consists of various strains related to three clonal lineages: type I, type II and type III, which differ in virulence and epidemiological pattern of occurrence (Howe and Sibley, 1995). *T. gondii* is one of the most well studied parasites because of its medical and veterinary importance. It is

used extensively as a model for cell biology of apicomplexan organisms (Kim and Weiss, 2004)

SPECIES AFFECTED

Cats are the definitive host where the mature parasite divides sexually in the intestinal mucosa. Cats are unique in the biology of the organism, serving as both definitive (intraintestinal life cycle) and intermediate (extraintestinal life cycle) hosts. *Toxoplasma gondii* can infect a wide variety of animals as intermediate hosts (extraintestinal life cycle), including fish, amphibians, reptiles, birds, humans and many other mammals. New World monkeys and Australian marsupials are the most susceptible, whereas Old World monkeys, rats, cattle, and horses seem highly resistant (Dubey, 2016).

TRANSMISSION

T. gondii is transmitted through three primary routes in cats: by ingestion of tissue cysts, by contaminated feed with oocysts from infected cat feces, or through congenital infection. It has adapted to be transmitted most efficiently by carnivorism in the cat and by the faeco-oral (oocysts) route in other hosts. Other minor modes of transmission include lactational and transfusion of body fluids (Saulsby, 2012).

EPIDEMIOLOGY

The estimated seroprevalance for *T. gondii* in domestic cats, worldwide, is 30-40%. Prevalence of toxoplasmosis in cats in different countries is enlisted in table l.

TABLE I: Prevalence of *Toxoplasmosis* in Cats (2011-2018)

Country	No of cats	No of positive cases (%)	Reference
Sri Lnka	86	26 (30.23%)	(Kulasena *et al.,* 2011)
India	11	24 (45.83%)	(Shah *et al.,* 2016)
United States	49	3 (6%)	(Lilly *et al.,* 2013)
South Africa	159	59 (37.1%)	(Hammond-Aryee *et al.,* 2015)
Brazil	265	32 (12.08%)	(Bolais *et al.,* 2017)
Iran	486	35 (7.2%)	(Tavalla *et al.,* 2017)
Korea	50	3 (6%)	(Kim *et al.,* 2017)
Pakistan	470	11 (2.3%)	(Nabi *et al.,* 2018)
Eastern China	180	39 (21.6%)	(Cong *et al.,* 2018)

INDIAN SCENARIO

Toxoplasma gondii antibodies have been demonstrated in cattle, buffaloes, camels, cats, dogs and other animals in India. The first report of *T. gondii* infection in animals was reported in rabbits by Krishnan and Lal in 1993 followed by reports of a dog suffering from toxoplasmosis by Ray and Raghavchari (Maharana *et al*., 2010). In India, the overall prevalence of toxoplasmosis in cats varied between 2.2% and 4.8% using the indirect haemagglutination antibody test (titre 1:64 or more). The prevalence of *T. gondii* in cats (2.5%) was low in India when compared with that in Western countries (Singh *et al.,* 2010).

PATHOGENESIS

Following ingestion of *T. gondii* (tissue cyst/bradyzoites) the intestinal cycle is completed. Cats may develop self limiting, small bowel diarrhoea which is presumed to be a reaction to enter epithelial replication of the organism (Lappin, 1999). The released bradyzoites from the tissue cyst or sporozoites from the oocyst penetrate the epithelial cells of the small intestine and multiply in the intestinal epithelium. After invasion of a cell the parasite multiplies and eventually fills and destroys the cells. Released *Toxoplasma* reach other organ though blood stream. The stage of parasitaemia begins about 5 days after infection and lasts until the development of immunity 2-3 weeks after infection (Parija, 2009).

Toxoplasma gondii is an intracellular parasite. It attacks most organs with predilection for the reticuloendothelial and nervous system. *T. gondii* may spread locally to mesenteric lymph nodes and to distant organ by blood. Necrosis in the intestinal and mesenteric lymph node may occur before other organ becomes severely damaged. Focal area of necrosis may develop in many organs, especially vital organ such as the eye, heart and adrenal gland. Necrosis is caused by cellular destruction as a result of intracellular growth of tachyzoites. By about the third week after infection, tachyzoites begin to disappear from the visceral tissue and may localize as tissue cyst in nervous and muscular tissue. *T. gondii* may persist longer in the spinal cord and brain because immunity is not able to penetrate the nervous tissue in comparison to visceral organs (Vegad and Katiyar, 2015).

In congenital infection, the main manifestations are encephalitis and febrile exanthema with pneumonia while enterocolitis is observed in acquired infections. However, vast majority of infections occur without any clinical signs. The characteristic granulomatous lesions are thought to be the result of hypersensitivity reaction. The pathogenesis of ocular toxoplasmosis may relate to reactions against the organism with immune complex formation and deposition in ocular tissues and delayed hypersensitivity reactions (Lappin, 1999).

Chronic, sublethal toxoplasmosis has been detected in cats both with and without FeLV or FIV coinfection (O'Neil, 2018). Fatal toxoplasmosis can either result from overwhelming primary infection or bradyzoites in tissue. Cysts may be induced to replicate rapidly and disseminate again as tachyzoites. Primary infection resulting in death generally occurs in immunodeficient cats such as transplacentally infected fetuses (Frenkel, 1988).

IMMUNE RESPONSE IN TOXOPLASMOSIS

Normally both antibody mediated and cell mediated immune responses occur on exposure to *Toxoplasma*. The antibodies together with complement destroy the organism found free in body fluids. Thus they reduce spread of organism between cells but have no effect on the

intracellular forms of parasite. Phagosome lysosome fusion does not happen in macrophages which phagocytose toxoplasma. As a result, *Toxoplasma* tachyzoites can grow inside macrophages, in environment free of antibodies or lysosomal enzymes (Vegad and Katiyar, 2015).

The intracellular organisms are destroyed by a cell mediated immune response. Sensitized helper 1 (Th1) T-cells secretes cytokines gamma- interferon (IFN-gamma) and interleukin-2 (IL-2) in response to *Toxoplasma* ribonucleoproteins. Besides microbicidal activities, IFN-γ if not controlled, might damage the intestinal integrity. Intraepithelial lymphocytes (IEL) are cytotoxic for infected enterocytes and might produce TGF-β that limits IFN-γ production (Tilahun, 2015). In addition, cytotoxic CD8+ T- cells can destroy *Toxoplasma* tachyzoites and *Toxoplasma* infected cells. Nonoxidative mechanisms, represented mainly by the production of nitrogen monoxide (NO) by macrophages activated by IFN-γ, are also involved during the chronic phase by inhibition of intracerebral parasite proliferation (Schluthess *et al*., 2008). IFN-γ also increases the activity of indoleamine 2, 3-dioxygenase, resulting in the breakdown of tryptophan, required for growth of the parasite (Waree, 2008). *Toxoplasma gondii* infection is not silent but induces rapid activation of transcription factors such as STAT-1 and NFkB. The parasite blocks nuclear translocation of both factors and macrophages cannot produce IL-12 or TNF-α and the parasite is able to evade or subvert the immune response of its host (Buzoni-Gatel *et al*., 2008).

CLINICAL SIGNS IN CATS

Clinical signs can vary, depending on the age of the animal, type of isolate, challenge levels, infectious stage of the parasite and areas of the CNS involved and may include depression, weakness, incoordination, tremors, circling, paresis and blindness. In cats, clinical toxoplasmosis is more severe in transplacentally infected kittens (Galvao *et al*., 2018). The most commonly affected organs are liver, lungs, central nervous system and eyes. Congenitally infected cats usually develop lethargy, depression, hypothermia, ascites with hepatitis, cholangiohepatitis, encephalitis, pneumonia and uveitis. In severe cases, sudden death occurs within a few days of life (Calero-Bernal and Genna, 2019). Uveitis occurs due to intraocular migration and replication of intracellular tachyzoites and deposition of immunocomplexes. Ocular form of the disease can occur without manifestation of other clinical signs in young cats infected transplacentally (Powell and Lappin, 2001).

In adult cats, non specific clinical system like hepatitis and abdominal involvement, hepatic failure and hyperplastic cholangitis can be observed. In addition, extra intestinal enteritis, inflammatory intestinal disease, thickening of the gastric wall due to eosinophilic fibrosing gastritis and regional lymphadenopathy are also observed. The disease may be rapidly fatal in cats with severe respiratory or neurological signs (Calero-Bernal and Genna, 2019) Pneumonia is the main sign of generalized toxoplasmosis. Acute respiratory distress syndrome and septic shock may occur in febrile cats. Less frequent findings, such as myocarditis with echocardiographic changes, diarrhea with oocysts or pyogranulomatous cystitis also reported (Evans *et al*., 2017).

LESIONS

Macroscopic pathology in cats

The organism most often affects the brain, myocardium, lymph nodes, lungs, intestinal muscularis, pancreas, liver, uterus and placenta. In brain, generally, myelitis, marked generalized mononuclear cell inflammation of the grey matter, non suppurative encephalitis and perivascular cuffing are common findings. Cases of intracranial granuloma and panencephalitis or non suppurative meningioencephalitis with glial granuloma have been also reported (Henriksen *et al*., 1994). Pulmonary lesions are severe in generalized toxoplasmosis observed in immunosuppressed cats. Multifocal necrotizing interstitial pneumonia with notable proliferation of type II pneumocytes along with infiltrates of macrophages and neutrophils is observed. Sometimes, small grey tumor like masses may be scattered throughout one or all lobes (Evans *et al*., 2017). Acute and multifocal necrotizing hepatitis and splenomegaly have been reported. The lymphnodes are usually enlarged several times their normal size, are firm in consistency and densely congested (Cohen *et al*., 2016).

Ulcers in the intestine, presumably resulting from necrosis of submucosal lymph nodules have been described in toxoplasmosis (Nagel *et al*., 2013). In addition, cutaneous manifestations with nodules that may ulcerate are sometimes related to feline immunosuppression (Anfray *et al*., 2005). Gross lesions in reproductive tract include, active hyperemia, rough and granular mucosae consistent with necrosis in uterus and fetal membrane (Saulsby, 2012).

Microscopic pathology in cats

The most commonly affected organs are the liver, lungs, central nervous system and eyes. In histopathological evaluation, the inflammatory infiltrates, predominantly composed of macrophages and neutrophils, with necrosis areas are observed in injuries involving nervous tissues of cats infected through the congenital route. These injured areas are usually discrete and multifocal, more often affecting perivascular spaces of the brain and spinal cord, followed by the cerebellum. Tissue cysts and areas of necrosis are rare and nodular gliosis occurs secondary to vasculitis, since tachyzoites replicate in capillary endothelium (Frenkel, 1988).

In lungs, the changes are particularly evident in the alveolar walls, whose lining becomes cuboidal or columnar and rich in cells, suggesting the appearance of fetal lung (so-called ‘fetalization of lung’). This feature also has superficial resemblances to pulmonary adenomatosis. The alveoli are filled with large mononuclear cells and leucocytes with aggregation of *Toxoplama* in the cells lining in alveoli. These lesions have a nodular distribution throughout the lung, appearing grossly as small grey, tumor like masses scattered throughout one or all lobes (Nagel *et al*., 2013). The myocardium is frequently invaded by *Toxoplasma*, which may be present in large or small groups within the cytoplasm of cardiac muscles cells (Evans *et al*., 2017). The liver in frank toxoplasmosis contains large, sharply

delimited, microscopic-sized areas of coagulation necrosis involving any part of the hepatic lobules. The necrotic areas, containing eosinophilic material and cell debries are surrounded by apparently normal hepatic cells with little or no cellular reaction. Tachyzoites may be found within liver in kupffer cells, in cysts containing a large number of organisms or singly or in pairs scattered sparsely in both the necrotic and viable tissue (Nagel *et al*., 2013).

The pancreas may be a site of localization in toxoplasmosis and here the acute necrotizing lesions arouse intense lymphocytic infiltration, edema and swelling (Cohen *et al*., 2016). Occasionally *Toxoplasma* invade the muscularis of the intestine, where a chronic necrotizing lesion followed by production of granulation tissue results in large, grossly detectable granulomatous nodules, which may replace the wall and impinge upon lumen. The organisms are clearly demonstrable in small and large group in the muscularis and the granulation tissue (Spycher *et al.,* 2011).

INFECTION TO OTHER SPECIES

There are no confirmed cases of clinical toxoplasmosis in horses and cattle. It is an important cause of abortion, embryonic death and resorption, fetal death and mummification stillbirth and neonatal mortality encephalitis and pneumonia particularly in sheep and goats (Tenter *et al*., 2000). Among companion animals, fatal toxoplasmosis may occur in dogs that are immune-suppresed following infection with concurrent distemper virus. There is fever with lassitude, anorexia and diarrhea (Tilahun, 2015). In pigs, clinical signs are rare but it can cause premature births, neonatal death and pneumonia with rare reports of myocarditis and encephalitis in most parts of the world (Dubey and Jones, 2008). Clinical toxoplasmosis in domestic poultry is rare, but has been reported with concurrent Marek's disease. Wild and zoo animals, New World primates, Australasian marsupials (kangaroos) and passeriformes (canary and finches) in captivity are highly susceptible to toxoplasmosis. Squirrel monkeys can die acutely with no prior signs. Severe ocular toxoplasmosis has been reported in finches (Castro and Dubey, 2019)

ZOONOTIC INFECTION FROM CATS TO HUMAN

Approximately, one-third of humanity is infected with *T. gondii* worldwide (Robert-Gangneux and Darde, 2012). Humans acquire their infections from ingestion of oocyst contaminated soil and water, from tissue cysts, by organ transplantation, blood transfusion, laboratory accidents or congenitally (O'Neil, 2018) An active *T.gondii* infection is dangerous especially for pregnant women and immune compromised individuals because these populations are at risk for reactivation of the *T. gondii* infection and development of life-threatening toxoplasmic encephalitis. The congenital form results in a severe systemic disease (Carruthers and Suzuki, 2007). Congenital toxoplasmosis may cause abortion, neonatal death, or foetal abnormalities, ocular disease with detrimental consequences for the foetus (Singh, 2016). Post natally infected humans can develop typical flu-like symptoms such as malaise, night sweats, sore throat and rash, retino-choroiditis, strabismus, blindness, pulmonitis, cervical lymphadenopathy, myalgia can also occur. However in more serious infections, *T.gondii* can infect neurons, and this could interfere with dopamine and glutamate mediated neurotransmission (Carruthers and Suzuki, 2007). It has also been suggested that this protozoan parasite could be a contributing factor to altering human behaviors such as increasing aggressiveness and impulsivity. *T. gondii* may also have a role in depression, anxiety, and most interestingly schizophrenia (Daniel, 2019).

DIAGNOSIS

Clinical signs of toxoplasmosis are not pathognomonic for a definite diagnosis. Hence, diagnosis is confirmed by biological, serological, histological or molecular methods or by some combination of the above (Pal *et al*., 2014). *T. gondii* oocysts are 10 µm in size and best demonstrated by centrifugation using Sheather's sugar solution (saccharose solution with a specific gravity of 1.27 g/ml) during the shedding period (Salant *et al*., 2010). A rapid diagnosis may be made by microscopic examination of impression smears of lesions with Romanowsky strain or giemsa stain. Tissue cyst wall can be stained with a silver stain and bradyzoites can be stained with periodic acid Schiff (PAS) staining. Electron microscopy, Immuno-histochemical staining of parasites with fluorescent or other types of labelled *T. gondii* antisera can aid in diagnosis. The IHC technique can be used to distinguish tachyzoites from bradyzoites (Dubey, 2016). The isolation of *T. gondii* by bioassay using laboratory animals (Mice) is generally considered as the gold standard for detection of *T. gondii* infection (Liu *et al*., 2015).

A variety of serological tests, such as Sabine Feldman dye test (DT), modified agglutination test (MAT), enzyme-linked immunosorbent assays (ELISA), immunosorbent agglutination assay (ISAGA), indirect fluorescent antibody test (IFAT) and indirect haemagglutination assays (IHA) can be used to detect different antibody classes or antigens (Lappin, 2010). In a study the sensitivity of ELISA ranged between 95.7% and 97.1% and the specificity between 97.3% and 97.6% (Gyorke *et al*., 2011). The Sabine Feldman dye test is highly sensitive and specific with no evidence for false results. It is a complement mediated neutralizing type of antigen antibody reaction. The major disadvantage of dye test requires live parasites and healthy human serum as an accessory factor, severely limiting the availability of the dye test (Sukthana *et al*., 2003). Nested PCR (n-PCR), quantitative real-time PCR (qPCR) of repetitive DNA sequences, multilocus PCR-RFLP, microsatellite, multilocus sequence typing (MLST) of single copy DNA sequences can be used for the diagnosis (Galat *et al*., 2018)

DIFFERENTIAL DIAGNOSIS

Clinical cases are frequently associated with immunosuppressive treatments. Differential diagnosis might be influenced by the geographical location where the clinical cases occur, for example, *Sarcocystis neurona* causing encephalitis and *Sarcocystis canis* causing hepatitis have been confined to America. Serum was tested for *N. caninum, T. gondii, Leishmania infantum chagasi* and *Leishmania amazonensis* IgG antibodies and only *T. gondii* antibodies were detected (IFAT titer=65,536).

DNA was extracted from the collected material and examined by nested PCR, confirming the diagnosis of *T. gondii* (Calero-Bernal and Genna, 2019).

PREVENTION AND CONTROL

1) Controlling the transmission between cats

To prevent infection in cats, they should never be fed uncooked meat, viscera, or bones and efforts should be made to keep cats indoors to prevent hunting. Trash cans also should be covered to prevent scavenging (Pal *et al*., 2014). It is also important to minimize opportunities for coprophagia by cats, along with the control of insects and rodents in the environment (More *et al*., 2018).

2) Prophylactic treatment of cats on risk and curative treatment of infected cats

Cats with suspected clinical toxoplasmosis should be administered supportive care as needed. Clindamycin hydrochloride administered (10 to 12 mg/kg, orally, every 12 hours) for 4 weeks or a trimethoprim-sulfonamide combination administered (15 mg/kg, PO, every 12 hours) for 4 weeks has been used most frequently to treat clinical feline toxoplasmosis (Maddison *et al*., 2008).

3) Vaccination

Live-attenuated vaccines based on mutants, such as T-263, TS-4 and S48 (Toxovax) have shown high efficacy in the prevention of shedding oocysts from cats. Live parasites require cold storage have a limited shelf-life and are accompanied by the constant risk of causing morbidity and mortality in vaccinates (Lau, 2018).

A recent study was done by Liu *et al*. (2017), on a DNA vaccine with the gene TgSOD from *T. gondii*. The vaccine triggered a stronger humoral and cellular immune response in the treatment group compared to the control group. This observation could become the foundation of a future vaccine that can prevent toxoplasmosis in cats. The latest experiments are based on crude rhoptry proteins adjuvant with Quil-A to immunize cats by the intranasal route (Hiszczynska-Sawicka *et al*., 2014).

CONCLUSION

All species have a particular tendency to suffer certain pathologies and not others, and cats, by their very nature as cats, are no different. The list of possible and frequently-occurring diseases that may arise if the conditions for a certain disease are met is long. Toxoplasmosis is the disease, which results from infection with the protozoan, *Toxoplasma gondii. Toxoplasma gondii* is a protozoan parasite that can infect all warm-blooded animals, reptiles and birds. However, its only definitive host is cats. As *T. gondii* is a zoonotic parasite, its behavior and shedding by domestic cats is of significant interest in human medicine. The infection rarely causes problems in healthy adults, although it can be dangerous to people with weakened immune systems. Toxoplasmosis is most dangerous to a developing fetus, possibly resulting in miscarriage, stillbirth or severe complications such as blindness and mental retardation. Despite years of study and human health concerns, there are still major questions unanswered regarding the lifecycle of *T. gondii*. While it is known that the period of highest shedding of oocysts is after the first infection, little is known about the natural immunity provided and how long it lasts.

Many aspects of the infection need to be addressed, both, in the feline and its transmissibility to humans. The disease needs to be explored more to establish its exact epidemiology and the effect on public health.

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