Zoonotic Infertility Due to Toxoplasma Gondii

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ABSTRACT

Toxoplasmosis is the infection of *Toxoplasma gondii.* It is an apicomplexan parasite that infects both animals and humans, worldwide. Its definitive hosts are felines. So, pet cats are the main toxoplasma reservoirs affecting the human population directly. Toxoplasma, resides in ovaries and hence leads to reduced reproductive potential, infertility, abortion or congenitally diseased offspring. Although famous for causing infertility in females, toxoplasma is also suspected to affect the male reproductive system. Besides causing infertility in humans, toxoplasma also affects the economics of the livestock industry. The main issues caused by toxoplasmosis are abortion, damage to the reproductive system and reduction in value of the breeding stock. In addition to the effect on reproductive health, toxoplasma is also suspected to greatly affect the brain and neurologic functions of the individuals with congenital infection. Conclusively, toxoplasmosis is a problematic disease that requires utmost care for control and prevention. Preventive measures including education of people about transmission routes and reservoirs should be implemented to control its spread effectively. Hygiene protocols should be developed and eradication measures should be taken to the reservoirs and transmission sources of toxoplasma.

Keyword: Toxoplasmosis, Feline, *Toxoplasma gondii*, Ovaries, Infertility.

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1. INTRODUCTION

An obligate apicomplexan parasite is *Toxoplasma gondii* famous for infecting both humans and animals all across the globe (Tonouhewa et al. 2017). The final hosts of this parasite are the cat family or felids. However, the latest research has shown the success of its development in mice when placed under certain conditions of inhibition by enzymatic action and modification of diet (Attias et al. 2020). The intermediate hosts of *T. gondii* include several types of birds along with terrestrial and aquatic mammals (Attias et al. 2020).

Toxoplasmosis is a disease of cosmopolitan factors found in humans and several types of mammals. Its etiologic agent is an opportunistic protozoan known as *T. gondii* mainly transmitted through oral route, acquired congenitally and by blood exchange. According to an estimate it has infected around 33% of the world's population (Tenter et al. 2000; Dubey and Jones 2008; Jones and Dubey 2010). Mostly in adult hosts it will not cause any serious issues. On the other hand, it can produce reduced mental functionality and loss of vision in children with congenital infection. It can also produce severe diseases in patients with disorders leading to compromised immunity. The latest research indicates that *T. gondii* infection is often discovered in association with the condition of abdominal hernia (Alvarado-Esquivel and Estrada-Martínez 2011). The plan of action followed by *T. gondii* for infecting hosts and transmitting the disease is multifaceted. Its life cycle pathway involves three stages of development of the parasite (tachyzoite, bradyzoite, and sporozoite) (Attias et al. 2020). The intermediate hosts of *T. gondii* include humans too. Humans can get infected by *T. gondii* through several transmission routes including

(i) Consumption of water contaminated with infective oocysts.

(ii) Consumption of vegetables and fruits grown in contaminated water.

(iii) Consumption of undercooked or raw meat infected with bradyzoites or tachyzoites of *T. gondii* (Dubey et al. 2009a).

(iv) Unsafe blood transfusion.

(v) Unsafe transplantation of organs contaminated with cysts or tachyzoites.

(vi) Congenital infection transmitted from the mother to the fetus via the placental route.

2. LIFE CYCLE

The definitive hosts of this parasite are the feline family that acquire the infection by carnivorism or ingesting the sporulated oocysts. However, ingestion of raw, non-pasteurized milk or milk products can also rarely serve as a potential source of *T. gondii* infection (Chiari and Neves 1984; Stelzer et al. 2019; Attias et al. 2020). Mussels and Oysters can act as host reservoirs for the infective stage of oocysts. These oocysts can later on produce infection after being ingested by other animals (Lindsay et al. 2004; Coupe et al. 2019; Monteiro et al. 2019; Attias et al. 2020). Being final hosts felids are responsible for harbouring the maturation stage of parasites that reside in their intestines. Once matured these parasites expel a large number of infective oocysts into the intestine. These oocysts are then passed out to the environment along with faeces. This release of infective oocyst can last from three to 18 days post-infection of the feline (Montazeri et al. 2020).

Progression in life cycle of *T. gondii* necessitates presence of both intermediate hosts and definitive hosts. Only if both hosts are available then life cycle of *T. gondii* (Fig. 1) will reach its completion after going through the asexual and the sexual phases of replication. The sexual portio of its life cycle progresses only in the intestines of the felids that are its definitive hosts. The infection in the intermediate hosts which includes the warm-blooded animals begins after they ingest oocysts contaminated foods or drinks. These are the same infective oocyst that were once released by a feline along with faeces (Montoya and Liesenfeld 2004). In the early few days of infection the actue phase

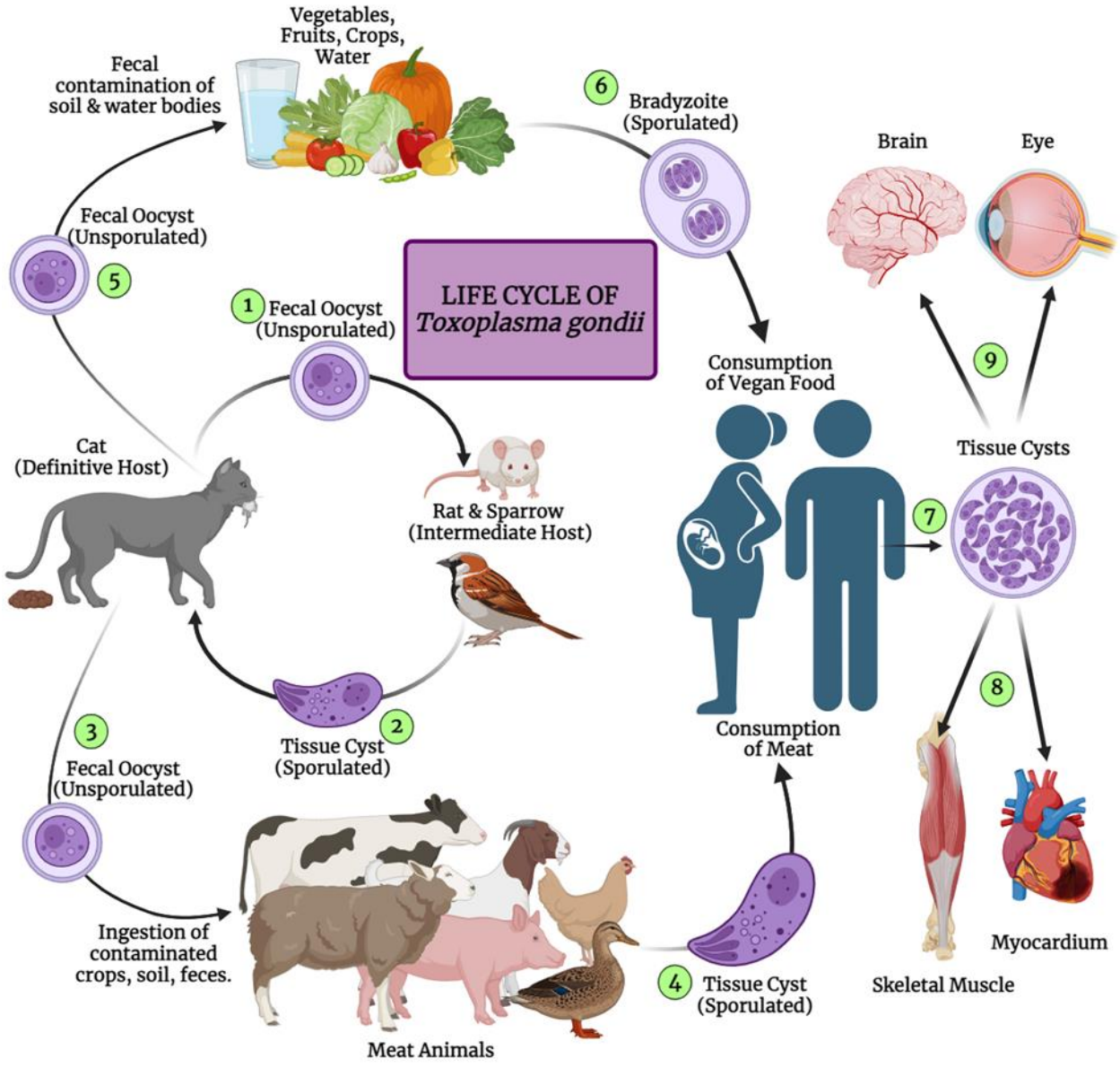

Fig. 1: Life Cycle of *Toxoplasma gondii*.

occurs marking rapid replication of the tachyzoites leading to an immense increase in their numbers The tachyzoites then mature into bradyzoites with the passage of time. Later on it begins to form tissue cysts that parasitize the cells of host. The toxoplasmosis infection may become lethal if it gains entry into an immuno-compromised patient, this situation will be aggregated by the reverse formation of tachyzoites from bradyzoites. Besides definitive hosts the intermediate hosts are also responsible for transmission of toxoplasmosis as they release tachyzoites and tissue cysts. Transmission pathways (Fig. 2) of toxoplasmosis include congenital, peroral and blood transfusion (Dubey 2010). The initial cases of human toxoplasmosis were reported in Jiangxi Province of China during the year 1964 (Xie 1964). Since the reports of first epidemic in China became public several human cases were also reported. This shifted the focus of researchers leading to the first epidemic survey launched for surveillance of toxoplasmosis.

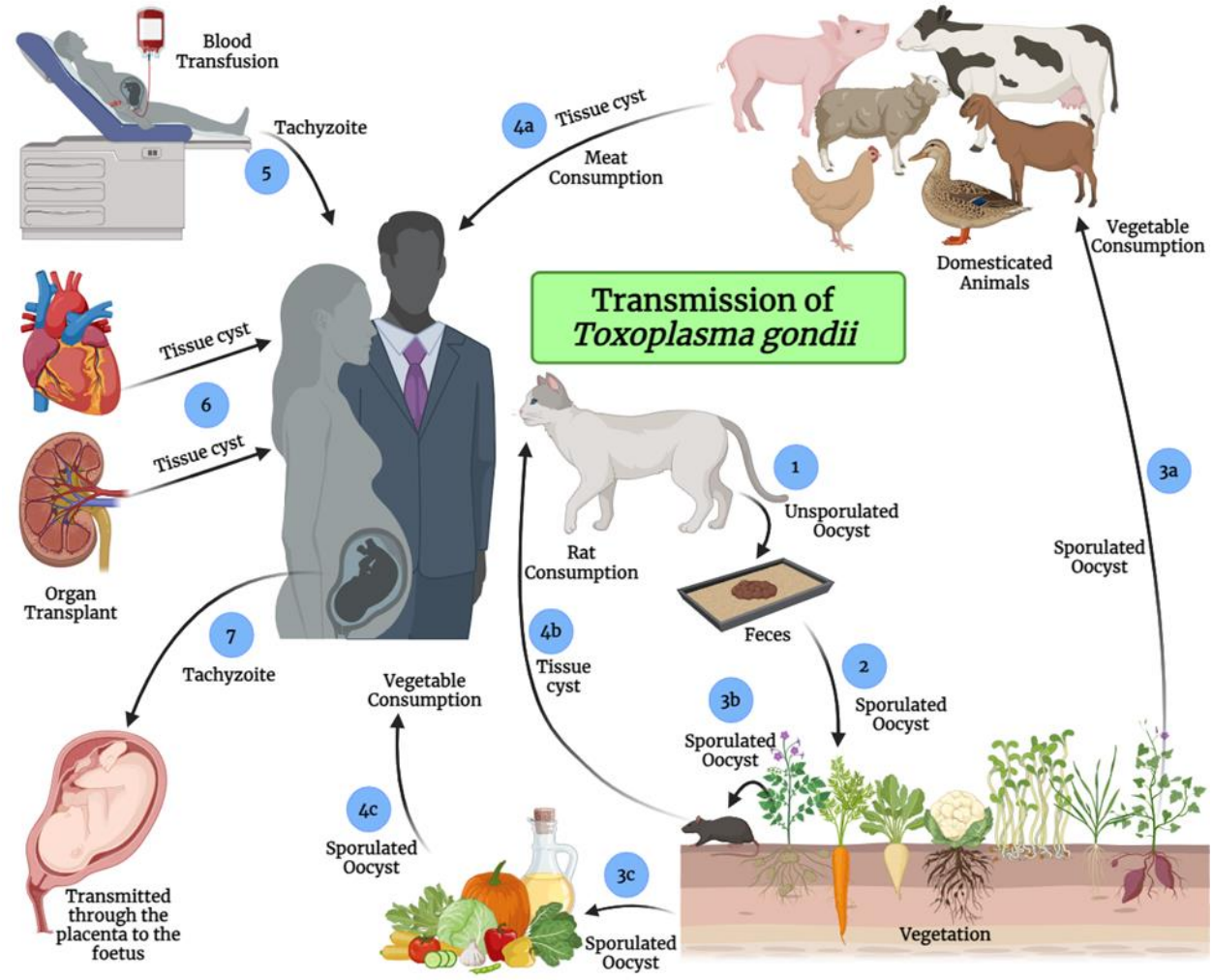

Fig. 2: Zoonotic transmission of *Toxoplasma gondii* via different routes.

This survey was initiated and performed during the year of 1978 in Guangxi Province of China (Chen et al. 2005). Despite these efforts the toxoplasmosis cases reported from China were barely recognized by the clinicians of the west as most of the information published from China was in Chinese and a small part of information was presented in English. The increasing incidence rate of *T. gondii* infections and a rise in the number of clinical cases was observed mostly (Xia et al. 2001; Li et al. 2002; Quan 2006) patients with impaired immune response systems. Similar trends were in patients that were congenital carriers of toxoplasmosis and psychosis. These reasons are enough to draw the attention of researchers to identify toxoplasmosis as a serious threat to the global public.

3. EPIDEMIOLOGY

Toxoplasmosis infection in animals or humans is caused by toxoplasma parasite that is prevalent worldwide. The rate of infection is variable as it depends on the geographical region of infection and the climate conditions of that area (Tonouhewa et al. 2017). Other factors affecting the prevalence of

toxoplasma infection include gender, age, geographic characteristics and contact with animals (Stelzer et al. 2019). Toxoplasma infections are often marked by inconsistent degrees of clinical symptoms that appear during infection. The state of clinical signs is dependent upon inoculum size and virulence of the parasitic strain that infected the host. Another dividing factor in this infection is the level of effectiveness of the host's immune response system (Mose et al. 2020).

4. PATHOLOGY

Toxoplasmosis has often been reported as a disease of the reproductive system. So, it mainly presents its infection symptoms by disturbing the normal reproductive parameters of the hosts. This disturbance appears as a negative impact on the reproductive functionality female host (Abdoli et al. 2012). Toxoplasmosis induces a programmed cell death cascade in the fundamental reproductive cells also known as the spermatogonial cells, through direct or indirect interference (Saki et al. 2020). This cell death cascade results in the reduction of sperm quality in humans as the number of main production cells is reduced (Zhou et al. 2003). Furthermore, reduced sperm quality also affects the fertility of male rats, when infected experimentally, by reducing it significantly (Terpsidis et al. 2009; Saki et al. 2020). Many researchers have reported a notable connection between the seropositivity of *T. gondii* and the occurrence of abortion in small ruminants. These reports originated from certain districts in the central region of central Ethiopia (Gebremedhin et al. 2013). In small ruminants like sheep, the toxoplasm infection may result in early embryonic death. After early embryonic death, the fetus may be disposed of by the body through resorption, fetal death, abortion, mummification, and stillbirth (Edwards and Dubey 2013). Such losses in the small ruminant industry ultimately lead to severe economic losses and affect the overall financial performance of the livestock industry (Tonouhewa et al. 2017; Etter et al. 2019).

The impact of *T. gondii* infections appears on the economics of the sheep rearing industry and other livestock business operations when the increased number of abortions leads to an increase in lambing/kidding interval of the livestock animals. Similarly, death and culling of infected animals lead to a reduction in milk production. Additionally, the presence of reproductive disease reduces the market value of the breeding stock. All these factors when combined together in the presence of endemic toxoplasmosis, lead to major economic losses for the livestock industry (Gebremedhin et al. 2013).

The stage of infection severity in the case of toxoplasmosis depends on the phase of gestation in which the ewe gets infected with the toxoplasma. Infection with *T. gondii* at the preliminary stage of gestation often leads to lethal consequences (Dubey et al. 2009b; Gebremedhin et al. 2013). In hosts with competent immune systems, the toxoplasma infection may persist asymptomatically. On the other hand, in the case of human hosts with impaired immune response systems such as in cases of disease like AIDS, the infection may turn into an ugly situation with dire effects and may lead to some serious problems (Frimpong et al. 2017; Etter et al. 2019). In the manner when this infection happens in women going through pregnancy it leads to the production of a fetus with congenital toxoplasmosis. A fetus that is congenitally affected by this infection faces increased severity of the disease along with elevated risks that are dependent on the time of maternal infection and are often accompanied by developmental malformation of the fetus, abortion, or reduction in quality of life for the child if it survives (Frimpong et al. 2017; Etter et al. 2019; Mose et al. 2020).

While toxoplasma is an agent with zoonotic disease transmission abilities it can be still controlled and prevented in both animals and humans all across the globe. These efforts to control toxoplasmosis are hindered in sub-Saharan regions of Africa due to several types of factors. The hampering factors include a lack of resources that in turn leads to high levels of poverty, the absence of proper diagnostic capabilities necessary for disease identification, limited abilities of disease surveillance bodies to operate

in that region, and poor practices regarding veterinary care (Hammond-Aryee et al. 2014). Having a proper implementation system in place for assurance of good veterinary practices is insanely crucial for the control of toxoplasmosis because its main reservoir is animals from which it can be transmitted to humans through the faecal-oral route and ingestion of undercooked or raw food or meat contaminated with Toxoplasma. These are the main transmission routes concerned with the transmission of infection in humans (Mose et al. 2020). All this pertains to the fact that effective control of toxoplasma infection necessitates raising enough awareness of good veterinary practices among veterinarians and relevant staff that they start practising proper protocols for personal safety and hygiene, improve their cooking and eating habits, monitor their intake routines and make corrections where needed, and lastly, they should emphasise accurate diagnosis of the disease so that factual disease reports can be presented to assess actual conditions of toxoplasmosis transmission and biological burden (Ramírez et al. 2017).

Correct diagnosis is very important for control and prevention of toxoplasmosis and it involves a few direct methods. The two main methods used for toxoplasma identification include molecular biology-based molecular techniques and immunology-based immunodiagnostic methods. The methods of direct diagnosis for toxoplasma infection involve the extraction of parasitic agents or bioassay, cell culture, and histology. The methods of immunodiagnostic include the immunofluorescent assay (IFA), Sabin–Feldman dye test (SFT), modified agglutination test (MAT), hemagglutination assay, enzyme-linked immunosorbent assay (ELISA), avidity, western blot, recombinant antigens, immunocytochemistry, and immunohistochemistry. The techniques of molecular diagnosis include Polymerase Chain Reaction (PCR), PCR-restriction fragment length polymorphisms (PCR-RFLP), real-time PCR, high-resolution melting (HRM) and loop-mediated isothermal amplification (LAMP) (Ramírez et al. 2017). Infection of *T. gondii* leads to initiation of IgM appearance in the host. The rise of IgM is followed by the emergence of IgA and IgE antibodies once an interval of about two weeks has passed since infection (Montoya 2002; Daka et al. 2015). The number of IgG antibodies begins spiking in the host after approximately four months have passed since the start of the infection. This elevated amount of IgGs then persists throughout the lifetime of the host (Daka et al. 2015).

Toxoplasma infection in a host individual with a competent immune response system resolves without any treatment (Muhie and Keskes 2014). On the other hand, the host individuals having an impaired immune system require dosing of antibiotics like clindamycin, sulfonamides, spiramycin, and pyrimethamine to be used for treatment of the infection (EFSA 2007; Vogel et al. 2010). The combination of drugs like sulfadiazine and pyrimethamine is suitable and effective for use in the treatment of newborns, infants, and pregnant women. Similarly, an antibiotic spiramycin has been proven effective for use in pregnant women to prevent congenital transmission of toxoplasma from an infected host mother to a healthy unborn fetus. It has been proven effective in preventing the infection but not for the treatment of latent infections as antibiotics do not have the capability to the bradyzoites in sufficient concentrations (Overton and Bennet 2010; Daka et al. 2015).

5. INFERTILITY IN WOMEN

In women, it has been experienced that there occurs no association between toxoplasmosis and sterility. However, some experiments have explained that *T. gondii* causes reproductive problems in mice species, and the main cause behind this problem was hypogonadotropic hypogonadism which is secondary to hypothalamic dysfunction, and during estrous cycling cessation, different histopathological changes were observed accompanied by impaired folliculogenesis and decrease in the development of corpus luteum (Stahl et al. 1994; Antonios et al. 2000). Spontaneous abortion, hydatidiform mole, stillborn, sterility and teras are the outcomes that are observed because of *T. gondii* exposure in pregnant women. Women

who have historically poor obstetric outcomes have seroprevalence of 14.2% (Zhang and Wang 2006) to 33.9% (Gong et al. 2006) which is much greater than the normal pregnancies that happen in China. A survey of 68 cases of oviducal sterility because of *T. gondii* showed a prevalence of 44.1%, which is too higher than that observed during normal pregnancies of women (3.3%) (Wei et al. 2005), clearly suggesting that oviducal sterility can develop because of *T. gondii* infections. Male sterility has also been linked to *T. gondii* infection. According to recent zoopery investigations, *T. gondii*-infected male rats exhibited a considerable rise in sperm abnormalities along with a significant drop in reproductive indices such as sperm motility and concentration (Terpsidis et al. 2009). When mice are experimentally infected with *T. gondii*, then similar results are obtained (Yang et al. 2005). (Zhou et al. 2002) discovered that toxoplasma transmission in sterile human spouses was higher than in fertile ones. This finding may have something to do with the increased levels of anti-sperm antibodies in toxoplasma-infected couples. In a recent study, 16% of 100 sterile males with *T. gondii* infection tested positive for IgM, and 13% tested positive for CAg, both of which are significantly higher than the percentage of healthy men (Qi et al. 2005). In Luoyang,Henan province, when seroprevalence of male sterility because of *T. gondii* was investigated, it was 19.8% (Yue et al. 2006), to 22.8% in Yan'an, Shaanxi province (Hui et al. 2003), again higher than that of detected in healthy men. The investigations and relevant studies in China suggest that *T. gondii* infection can be a cause of male sterility (Lu 1998).

Preventing direct contact with infection sources, such as cats, contaminated settings, eating raw or undercooked meat, maintaining good personal hygiene, and washing hands, is the main strategy for preventing toxoplasmosis (Daka et al. 2015). The other strategy for disease control is to eliminate mechanical vectors responsible for transmission, such as flies, cockroaches, and rats in the surrounding environment (Muhie and Keskes 2014).

6. TOXOPLASMOSIS INFECTION AND BEHAVIOURAL CHANGES IN ANIMAL

Latent infection of *T. gondii* can affect the performance of the central nervous system especially in a young growing body. This phenomenon backs the claims of neurologic changes occurring in toxoplasmosis in animals. This evidence can be also used to support the reports of behavioural changes appearing in animal models experimentally infected with latent toxoplasmosis. Observation of the toxoplasma-infected rodents served as strong evidence of reduced learning, poor memory task achievements and poor performance although to the researcher's surprise, no cysts were seen in the hippocampi of infected animals. On the other hand, several cysts were discovered throughout the brain. These occurrences suggest that the alteration in neurophysiology serves as the basis for anomalous behaviour shown by the infected animals (Daniels et al. 2015). Several researchers have reported observations of similar changes in the behaviour of the infected mice and cats (Joanne 2007). The changes were interpreted by reporting researchers as a manifestation of the invading parasite's neurotrophic manipulative function performed for the completion of its life cycle. The altered behaviour of rodents makes them more prone to be preyed upon by cats making this a cascade fall to the definitive hosts of the parasite. Recent research has now revealed that initiating treatment against *T. gondii* can resolve behavioural alterations bringing it back to normal. These reports provided the researchers with new avenues for managing cases of human schizophrenia (Zhu et al. 2003; Joanne 2007).

7. DETECTION OF *T. GONDII* OOCYSTS IN FAECAL SAMPLES

The discoveries unveiled in this study were unique from reports of other authors (Dabritz et al. 2007; Bizhga 2017). In the region of Bangladesh, the number of well-organized animal farms is limited and cats

can be seen wandering everywhere in the areas where study was being conducted. The wandering of stray cats meant the contamination of the grass or pasture. So a strategy was developed to keep the livestock like cattle, sheep and goats confined within the enclosure or pasture for grazing. This strategy reduced the risk of infection that they could get from the environment contaminated with sporulated oocysts of *T. gondii* being shed by cats through faeces. This reduces the chances of people getting an infection after ingestion of raw or undercooked meat of these animals. Additionally, it is rare because of the food habits of Bangladeshi people who cook everything well before consumption. On the other hand, people may get infected by consuming unwashed fruits and vegetables as they might be contaminated due to the environment of the kitchen garden where they were present along with sporulated oocysts. People can get infected accidentally while they are working in situations to come in contact with infective oocysts like gardens and fields etc. During warmer seasons (March to June) toxoplasmosis displays a higher prevalence. Contamination Soil by *T. gondii* oocysts is not a stagnant event as it can differ depending on the presence of excreta of a feline with oocysts in a faeces environment with climate conditions such as moisture and temperature (Dubey 2004; Casartelli-Alves et al. 2015). Various reports have verified a connection between outbreaks of toxoplasma infection and contamination of water bodies toxoplasma oocysts (Cook et al. 2000; Dubey 2004; Karanis et al. 2013; Krueger et al 2014). Once the soil becomes contaminated with oocysts, the oocysts may reach the water body source by wind or rain and then water becomes contaminated. Adult cats were affected more than young (<4 months old) by this protozoa. It is expected that with increasing age, the exposure of cats to *T. gondii* infection also increases (Miro et al. 2004; Alvarado et al. 2012). This may be due to feeding cats with raw meat and infrequent cleaning of the litter box (Besne Merida et al. 2008). Young cats might get infection via congenital transmission from infected dams or from milk.

All of the studied cats were free-roaming but with limited access to households and none had a specific owner. In general street cats are more prone to *T. gondii* infection compared to household cats because street cats could acquire the infection through catching rodents, birds, reptiles and raw food scraps (Sah et al. 2019).

8. CONCLUSION

Toxoplasma gondii is an apicomplexan and obligate parasite. Its life cycle is divided into several hosts including warm blooded mammals as intermediate and felids as the definitive hosts. It resides in intestines of feline hosts and matures into infective oocysts that can be then expelled through feces. It can spread among hosts through oral route as by consumption of contaminated edibles, blood exchange and congenitally. Although toxoplasma infection is unable to cause much damage in normal adult hosts. In adult hosts it persists asymptomatically. On the other hand, its congenital transmission in the fetus can produce some serious symptoms in the host, especially one related to abnormal neurological behavior. These anomalies may include reduced brain performance, poor memory and inability to achieve tasks. It affects memory despite having cysts in hippocampi.

Toxoplasmosis also affects the farmers economically besides its disease impact. The losses occur in the form of abortions especially in sheep and loss of breeding stock value due to reduced fertility and gestation disorders. Toxoplasma affects fetuses because it survives in ovaries and has high chances of transmission to the fetus during pregnancy leading to early embryonic death which can further aggravate into abortion, mummification or maceration. It can be easily controlled for saving fertility of women by teaching them proper hygienic measures, eliminating hosts like pests and flies, preventing contact of pet cats with toxoplasma.

Additionally, it can also affect the fertility of males. In contrast to normal young adults it severely affects the adults with impaired immune system as in case of acquired immunodeficiency syndrome (AIDS) or such similar diseases. Its prevalence increases in summer as compared to winter. Toxoplasmosis, although problematic can be easily controlled by educating people to cook food properly before consumption, stay away from unsafe blood transfusion and follow proper treatment protocols for preventing its transmission.

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