Toxoplasmosis: a global zoonosis

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Abstract:

Toxoplasma gondii (T. gondii) is an obligate intracellular parasite historically recognized as the cause of human congenital toxoplasmosis. Recently, it has been the target microorganism of scientific research due to its unbelievable biological characteristics. Although it is traditionally studied because of its zoonotic potential, which enabled it to chronically infect about one third of the world's human population, *T. gondii* is of high interest for veterinary medicine. In careless handling it easily causes contamination of meat and meat products, as much as it causes the vast losses in cattle breeding. Today, transmission by the members of the Feline species is no longer considered the primary source of the infection. Nevertheless, it is obvious that the primary source of transmission in humans are unwashed herbal food or undercooked meat. Results of recent research point to the ability of *Toxoplasma* to induce special neurological response in its host, increasing its infective potential. Furthermore, there are indices that latent existance of toxoplasma in its host induces an array of neurological and psychiatric conditions ranging from affective and cognitive dysregulations, through Parkinson's and Alzheimer's disease to schizophrenia.

Key words: toxoplasmosis, pregnancy, congenital infection, cat, zoonosis

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Introduction

Toxoplasma gondii is to some extent infective to all warm-blooded animals and humans (Dubey, 1996; Elmore et al., 2012). There are strong scientific indices that *T. gondii* has infected more than one third of the world's human population, therefore making the parasite one of the most successful ones on Earth (Saeij and Frickel, 2017). Studies show that 30 to 50 % of the global human population are the carriers, and most people's immune system never deliberates from this highly contagious protozoa (Parasites – Toxoplasmosis, CDC, 2018). About 85% of women in reproductive age in the United States are potential hosts to the accute primoinfection (ACOG, 2000). Congenital toxoplasmosis, beside being the disease of the immunocompromised patients (Opsteegh et al., 2015), leaves the most severe sequelae which may lead to severe dissabilities or even death (Marr, 1992; Luft and Remington, 1994). It is estimated that globally about 200.000 new human cases of congenital toxoplasmosis occur each year. Only in the United States the statistics vary from 400 to 4000 new cases of congenital toxoplasmosis annually (Jones et al., 2014).

T. gondii is highly infective for several animal species, especially the small ruminants, ewes, goats (Santana et al., 2010) and swine (Wallander et al., 2016). Dogs (Rijks et al., 2016), cats (Brennan et al., 2016; Teutsch et al., 1979), horses (Akca et al., 2004) and camels (Chávez-Velásquez et al., 2014) are easily prone to the infection as well. Toxoplasmosis is widespread in wild animals in different mammal species (Alvarado-Esquivel, 2013), including the marine mammals (Van de Velde et al., 2016), which are in great risk of severe forms of the disease (Barbieri, 2016). Toxoplasmosis is described in another species, but it is still seldom noted in birds and reptiles. In domesticated animals Toxoplasmosis causes abortions, stillbirths, neonatal deaths and generalised illness, which often appear in outbreaks (Verma et al., 2016).

Toxoplasmosis is usually acquired through consumption of uncooked meat or by uptake of cat-shed parasite from the soil or water (Mead et al., 1999; Vogel et al., 1996), contaminated food or the cat litter (Choi et al., 1997; Sacks et al., 1983). Case control study from six large European cities showed that inadequately cooked or cured meat was the main risk factor for infection with toxoplasma in all centers. Between 30% and 63% of infections in different centers were attributed to consumption of undercooked or cured meat products and 6% to 17% to soil contact (Cook et al., 2000). According to the American Veterinary Medical Association, infected cats shed the eggs only for one or two weeks during their lives, right after their first exposure to the parasite. Like humans, cats rarely have symptoms when first infected, so most people don't know if their cat has been exposed to *Toxoplasma*. Because of its fastidious nature, the passing of non-infective oocysts and the short duration of oocyst shedding, direct contact with cats is not thought to be a primary risk for human infection (Acha and Szyfres, 2003; Jones, et al., 2001).

The primary infection with *Toxoplasma* is usually presented in the form of a mild flu-like disease (Alford et al., 1974) in otherwise healthy both humans and animals, and it often passes unrecognized (Rico-Torres et al., 2016). Encysted parasites can survive for a very long time, perhaps lifelong, in the tissues of most or all hosts.

Some clinical cases result from new exposures to *T. gondii*; others occur while parasites in the tissue cysts become reactivated when the host looses its immunocompetence (Gurry, 2017). Recently, severe and life-threatening infections among immunocompetent people in tropical Africa were discovered bringing to light the possibility that some unusually virulent strains of *T. gondii* may exist in this area (Sobanski et al., 2013). Only the symptomatic toxoplasmosis in humans should be treated because of serious side-effects of the medications.

Toxoplasma has an unusual ability to infect any warm-blooded animal cell, from immune cells to brain and muscle cells due its incredible potential to steal and utilize a range of energy-rich nutrients from the host cell, allowing it to adapt to different host cell niches (Aubert et al., 2010). Recently, it is connected with series of behavioral changes from recklessness to neuroticism. There are strong evidences that T. gondii can be implicated in the etiology of attention deficit hyperactivity disorder (Fabiani et al., 2015), epilepsy (Ngoungou et al., 2015), depression, and even schizophrenia (Yolken, et al., 2015), but a causal relationship has not been established yet (Opsteegh et al., 2015).

Felides and their role in the biological cycle of *Toxoplasma gondii*

Domesticated cats who are the members of the Felidae familyare the final or integral hosts for *T.gondii.*, because, as has been found, they are the only species where *T. gondii* can sexually reproduce (Hartmann et al., 2013). When it comes to other warm-blooded animals they are playing the role of the intermediate hosts (Hill et al., 2005). Four major forms of *T. gondii* are generally recognized: the oocysts, which are spilled in the feces of the final host (containing sporozoites after sporulation); the tachyzoites, organisms found in the rapidly multiplying tissues ;the bradyzoites, organisms found in the slowly multiplying tissues ; and the tissue cysts, walled structures that contain the bradyzoites (Frenkel and Fishback, 2000). While being in the intermediary hosts, *T. gondii* goes through an asexual reproductive cycle. After the animal eats the parasite from the tissue cyst originating from the raw or poorly cooked meat and viscera of the infected animal, or the oocysts originating from the cat feces, the wall of the cyst dissolves during digestion, and the bradyzoites or sporozoites are being released. These organisms enter the small intestine to the lamina propria and begin to multiply as the tachyzoites. Tachyzoites can disseminate to extraintestinal tissues within a few hours of infection via the lymph and blood. They are capable of entering almost any cell and multiply What happens to the host cell is that it eventually ruptures and the released tachyzoites enter the new cells. As host develops resistance, the tachyzoites start to disappear forming the bradyzoites within the tissue cysts (Dubey et al., 1998). Tissue cysts can be found in many organs, but they are usually found in skeletal muscle, myocardium, CNS and the placenta (Wilson and McAuley, 1999). Generally, there is no host reaction, and the tissue cysts can persist for many years, possibly lifelong. Traditionally, the bradyzoites in the tissue cysts have been viewed as "resting," but the new research suggests that they continue to replicate (Montoya and Liesenfeld, 2004). Tissue cysts occasionally rupture and release parasites, which are readily controlled by the immune system of the immunocompetent individuals, but they may multiply and spread if the host becomes immunosuppressed. Toxoplasmosis is more often reactivated rather than newly acqired in AIDS patients (Kasper, 1998). Many clinical cases of older or immunosuppressed cats are also thought to result from reactivated infections.

In Felidae, the parasites simultaneously undergo a sexual replication cycle (Holzworth, 1987): some of the parasites multiply in the intestinal epithelial cells where they initiate a sexual cycle (gametogony), which results in formation of an unsporulated oocyst. Oocysts are shed in the feces, and the prepatent period lasts 3-21 days in domesticated cats. They appear earlier (3-10 days) if the cats are infected via the tissue cysts rather than the oocysts. The oocyst sporulates in the environment forming two sporocysts, each with four sporozoites. Sporulation occurs in 1 to 5 days under ideal conditions, but can take up to several weeks depending on aeration and temperature, at which time it becomes inffective. When a susceptible animal ingests the sporulated oocysts, the sporozoites penetrate the intestinal lining, become the tachyzoites and a new cycle of the parasite is established. Most cats excrete oocyts during 1-2 weeks, although shedding for up to 3-4 weeks has been reported. Cats usually shed oocysts only on their first exposure to *T. gondii*, and seem to be resistant to reinfection; however, experiments have demonstrated that re-infection and re-shedding are possible under some conditions (Brennan et al., 2016).

For the decades, the cats were accused to be the main reason of congenital toxoplasmosis. Pregnant women were strongly advised by their health professionals to avoid any contact with cats, or even to give away their feline pets (Stagno et al., 1980; Teutsch et al., 1979). Although modern attitudes regarding the weak potential of infection originating from the direct contact with cats do not support the reduction of the contact with feline pets, the problem still exists with the excretions of the non-domesticated cats (Basso et al., 2005). Furthermore, certain animal populations are highly endangered with increased number of feral cats, either from their unbalanced hunt, or the risk from infection (Hooshyar et al., 2007; Barbieri et al., 2016). Therefore, the strong voices are raised against the stray and feral cats accused to contaminate human and animal environment with the Toxoplasma oocysts. There were intensive polemics regarding regulation of the cat population between the conservation biologist groups and animal-friendly organizations, ranging from trap-neuter-return solutions to the euthanasia of the whole feral cat colonies. Neither solution has proven successful in changing the toxoplasmosis incidence on the global level (Rouatbi et al., 2019) The number of infectious oocysts in the environment depends on the feline population size, incidence of *T. gondii* infection in felines, the number of

oocysts shed by an infected feline (Bauer et al., 2013; Gomez-Marin et al., 1997), a fraction of the oocysts that end up in the environment and sporulate, and survival of the infectious oocysts (Dabritz and Conrad, 2010). Cats become infected usually by hunting or eating the raw meat (Opstegh et al., 2012). In order to reduce the number of caught prey animals, the cat can be kept indoors, especially at night. Vaccination of cats may be a more effective way of reducing oocysts shedding by cats. However, there are currently no vaccines commercially available. Vaccination of stray cats is only feasible when a capture program is in place.

Infection in humans

More than 60 million people in the U.S., and up to 95 percent of people in some areas of the world may be infected, according to the U.S. Centers for Disease Control and Prevention (Parasites – Toxoplasmosis, CDC, 2018). It is most commonly found in areas with hot, humid climates and situated in lower altitudes (Walton et al., 1966). However, most immunocompetent, non-pregnant people infected with *T. gondii* didn't develop any symptoms (Harker et al., 2015). Approximately 10-20% of the infected people develop lymphadenitis or a mild, flu-like syndrome with symptoms like fever, malaise, myalgia, headache, sore throat and lymphadenopathy. Some patients may also have gastrointestinal signs and/or a rash, and in some cases, the disease may show symptoms similar to infectious mononucleosis. Most people recover without treatment within several weeks to several months (Leal et al., 2007). More severe, ocular toxoplasmosis tends to be seen in adolescents and young adults (Maenz et al., 2014; Pfaff et al., 2014). Some cases are a delayed consequence of congenital infection, but some result from postnatal infections, including ones that were recently acquired. There are two types of lesions: unilateral or bilateral. The typical presentation is chorioretinitis, which often resolves within a few weeks to a few months in immunocompetent patients, leaving a retinal scar (Ozgonul et al., 2017; Pleyer et al.,2014). Serious disseminated illness or organ involvement can happen in immunocompetent people, but rarely. Some reported cases include myositis, myocarditis, hepatitis, pneumonitis and focal or disseminated neurological signs (Casagrande et al., 2015). The clinical signs of severe disease may include high prolonged fever, hepatomegaly, splenomegaly, lymphadenopathy, headache and a dry cough with chest pain, often progressing to dyspnea (Carme et al., 2009). Toxoplasmosis can develop into a severe disease in immunosuppressed people (Mitchell et al. 1990; Minkoff et al., 1997). HIV-infected patients with a low CD4+ T cell count tend to develop CNS signs, especially when the illness is caused by reactivated tissue cysts from an earlier infection (Wallace, 1993; Fong et al., 2010).

Toxoplasmosis and pregnancy

Epidemiological studies recording prevalence of *T. gondii* infection in pregnant women around the world indicate considerable variation between the countries (Robert-Gangneux et al., 2015) ranging, for example, from 9% to 67% in European countries (Stray-Pedersen and Lorentzen, 1980; Ljungstrom et al., 1995; Joynson, 1992), and reaching as high as 92.5% in Ghana (Ayi et al., 2010) Tanzania (Doehring et al., 1995), Nigeria (Onadeko et al., 1992) and Kenya (Bowry et al., 1986). Similarly, high prevalence of *T. gondii* infection has also been found in some American countries (Sousa et al., 1988; Bittencourt et al., 2012; Monsalve-Castillo et al., 2012; Ramsweak et al., 2008; Reboucas et al., 2011). In contrast, prevalence was relatively low in East Asian countries, especially in Korea (Song et al., 2005) and Japan (Sakikawa et al., 2012). In the U.S, one out of thousand babies on average is born with toxoplasmosis each year. 90% of infected babies appear normal at birth, and 55-85% of them develop symptoms months to years later, suffering from eye infections, hearing loss and learning dissabilities (Carter and Frank, 1986; Wilson et al., 1980).

With rare exceptions, women who have been infected at least 6 to 9 months before conception develop immunity to and do not pass it on to their fetuses (Foulon et al., 1999). Once infected with toxoplasma, the woman would ussually not become infected again (Mittendorf et al., 1992). Serologic testing on toxoplasmosis is not an intergral part of antenatal care worldwide (Koskiniemi et al., 1992; Eskild et al., 1996). The American College of Obstetricians and Gynecologists (ACOG) does not recommend routine screening in pregnancy. Screening may lead to equivocal or false-positive test results which could lead to inappropriate treatment (Jones et al., 2001). However, if tested and positive, the pregnant woman has probably been infected in the past. Even if exposed again in the current pregnancy, her unborned child will not be affected. If negative, some precautions should be taken (Remington et al., 2006).

Acute toxoplasmosis in pregnancy is often accompanied by miscarriages, stillbirths and severe birth defects like blindness, cerebral palsy and mental retardation (Alford et al., 1974; Kimball, et al., 1971). The disease is more serious if passed on to the fetus in the first three months of pregnancy (Dunn et al., 1999). However, it is more commonly transmitted later in pregnancy (Hide, 2016). According to the U.S. Organization of Teratology Information Services (OTIS), when the mother gets infected between week 10-24 of pregnancy, the risk for severe defects in the newborn is about 5-6%. Effects on the infant include premature birth, low birth weight, fever, jaundice, abnormalities of the retina, mental retardation, abnormal head size, convulsions, and brain calcification (Kapperud et al., 1996; Cook et al., 2000). During the third trimester, a fetus has an increased risk of becoming infected, but the risk of damage to the fetus is decreased since most of the important development has already occurred (McAuley, 2014). Manifestations of congenital toxoplasmosis may not become apparent until the second or third decade of life (Başaran et al., 2014).

It is still not clear how *T. gondii* acts in development of different detrimental effects on the fetus and newborn.

Recent research points to the role of interferon, the bioactive agent which the body produces in response to several viral and parasitary infections. It is estimated that 10 to 20 percent of pregnant women miscarry during their first trimester of pregnancy. Slow fetal growth may also arise as a result of maternal infection with certain microbes, parasites or viruses (such as toxoplasmosis, or infection with Rubella virus, Cytomegalovirus, Herpes or Zika viruses) or because of genetic or autoimmune diseases (Liu et al., 2009). Recently, scientists have identified a new cellular mechanism that alters placental development, potentially causing serious complications during pregnancy. It seems that the high levels of interferon impair the ability of sinciciotrophoblast to form the protective shield between the mothers' immunocompetent cells and the allogenic fetal tissues (Buchrieser et al., 2019). Elevated levels of interferon are also observed in some other pathologic conditions of high-risk pregnancies like in autoimmune or inflammatory diseases such as lupus, preeclampsia and early spontaneous abortion. Specifically, interferon induces the production of a family of cellular proteins known as interferon-induced transmembrane proteins (IFITMs), which block the fusion activity of syncytin, a protein which mediates the sinciciotrophoblast cells fusion (Bolze et al., 2017). IFITM proteins are beneficial since they prevent viral fusion with the cellular membrane, thereby stopping viruses from entering and multiplying within the cells. However, in interferon excess the IFITM proteins are produced at a significant level in the placenta, which is the potential clue for the harmful side effects (Buchrieser et al., 2019).

Serologic tests are used to diagnose accute infection in pregnant women, but the false-positive results occur frequently. IgM-specific tests and/or paired IgG titers are performed to define the time of exposure. A negative IgM test suggests that the infection is not recent, however, a positive test can be difficult to interpret. While it generally suggests recent exposure or ongoing active infection, IgM titers occasionally persist for more than two years in healthy individuals (Jenum et al., 1997). Conversely, IgM may be absent, especially during reactivated infections in immunosuppressed people (Dhakal et al., 2015). Therefore, serologic diagnosis must be confirmed at a reference laboratory before the treatment with potentially toxic drugs. Side effects of treatments must be considered when treating pregnant women. Toxoplasmosis in pregnancy is traditionally treated with spiramycin, both as preventive and curative drug. It is a macrolide antibiotic that can cause gastrointestinal and dermatologic reactions. Sulfonamides have been associated with kernicterus in the newborn when given in late pregnancy. Pyrimethamine is not generally recommended for pregnant women because it is a folic acid antagonist (FDA category C), and connected with the heart and kidney malformations in infants. It may increase the risk of central nervous system cancer in childhood. Therefore, pyrimethamine and sulfadiazine treatment before 18 weeks of gestation should be discouraged. Both drugs also carry a risk of bone marrow suppression. Application of these medications mandates folic acid supplementation (Jones et al., 2001).

New insights into biological potential of *T. gondii* in humans

Like many other parasites, T. gondii resides within specialized vacuoles inside the infected host cells, but the process by which peptides from the trapped parasite are processed by the infected cells and presented to killer T cells is still not clear (Uboldi et al., 2015). The parasite gets noticed by the immune system when the membrane of the vacuole fuses to the endoplasmic reticulum, which presents the pathogens to T cells, allowing a swap of parasitic peptides (Butcher et al., 2011). The infected host fights back by production of the human protein called ubiquitin, which tags the vacuole for destruction via the cell's acidification system. Ubiquitin tagging leads to vacuole-lysosome fusion in the human cells infected with toxoplasma (Clough et al., 2016). Another possible way of combatting the parasite goes through activation of killer T cells. They become activated when the toxoplasma-infected cells produce interferon-γ (IFN-γ) (Lee et al., 2015). Furthermore, it has been observed that the parasite takes control and forces immune cells around the body to spread it, eventually reaching the brain: after ingestion of the parasite, during the passage through the intestinal wall it contacts the immune cells that would normally kill it (Denkers et al., 2012). Instead, immune cells become Trojan horses (Lima, et al., 2019). A new calcium receptor on immune cells was found, acting as a mailbox to receive the parasite's orders for the cell to move, using calcium molecule as the messenger in the communication. On the other hand, it was discovered that toxoplasma quiets its host's alarm system by blocking immune cells from producing certain cytokines, proteins that stimulate inflammation (Martynovicz et al., 2019). Specifically, toxoplasma produces a ROP16 protein which infiltrates the communication channels in immune cells, causing them to lower cytokine production. In their recent study, Fuks et al. (2012) showed for the first time how the parasite entered the brain and increased the release of a neurotransmitter GABA (gama-aminobutyric acid) which, amongst other effects, inhibited the sensation of fear and anxiety. Human dendritic cells, a key component of the human CNS immune defense, when experimentally infected with toxoplasma actively release GABA (Brooks et al., 2015). Upon invasion, a signaling cascade is activated via chloride channels, GABA channels and calcium signaling that mediates the migratory activation of the infected immune cell (Kantani et al., 2017). A series of studies have previously shown that the parasite affects the brains of infected rats so that they lose fear of cats and even become attracted to cats' scent (House et al., 2011), making them an easy prey (Ingram et al., 2013). The parasite spreads by ensuring that the rat is eaten by a cat. Chronic infection with the parasite Toxoplasma gondii can make mice lose their innate, hard-wired fear of cats. This loss of their innate fear may persist after the parasite is no longer detectable in their brains, suggesting

that initial infection may cause permanent changes in the mechanisms underlying fear of predators (Pittman et al., 2015). Surprisingly, several studies in humans and mice have suggested that even in the dormant phase, the parasite can influence behavioral and personality shifts. There are several studies showing that T. gondii has an impact on mental illnesses such as schizophrenia and depression and anxiety disorder, with the disorders being more common in people who are carriers of Toxoplasma gondii (Webster et al., 2013, House et al., 2011). Further, the parasite was shown to also affect aggressive or risky behaviour (Johnson et al., 2018). Moreover, the parasite secretes an enzyme tyrosine hydroxylase, necessary for the dopamine production (Tedford and McConkey, 2017). Dopamine is a natural chemical which relays messages in the brain controlling aspects of movement, cognition and behaviour. It helps control the brain's reward and pleasure centres, and regulates emotional responses such as fear (Martin et al., 2015). The presence of a particular kind of dopamine receptor is also associated with sensation-seeking, whereas dopamine deficiency in humans results in Parkinson's disease. Dopamine's role in mood, sociability, attention, motivation and sleep patterns is well documented. Schizophrenia has long been associated with dopamine. Hence, the majority of blockbuster drugs in the market target dopamine receptors. The presence of parasite in the infected brain cells increases the dopamine levels by impacting encoding of the enzyme responsible for dopamine production (Prandovsky et al., 2011). Based on these analyses, it is clear that T. gondii can orchestrate a significant increase in dopamine production in neural cells. On the other hand, the recent research led by Eun-Hee Shin of the Seoul National University College of Medicine found that this immune system suppression had positive effects on Alzheimer's disease in mouse models, resulting in a significant decrease in the amount of b-amyloid plaque deposition, a hallmark of Alzheimer's disease, and better performance in behavior tests (Jung et al., 2012). These intriguing biological characteristics of the parasite T. gondii make it extremely interesting for researchers, due to its invasiveness on humans and animals (Van Vormer et al., 2013), and its conection with several pathological conditions in humans which are under intensive study.

Infection in animals

Significance of T. gondii in veterinary medicine became clear in several outbreaks which devastated the livestock in Australia and New Zealand (Brennan et al., 2016; Dubey, 2009). More recent, the outbreaks were described mainly after global use of arteficial insemination in sheep with potentially contaminated semen (de Moraes et al., 2010; Wanderley et al., 2013). T. gondii usually infects adult sheep and goats without clinical manifestation, however, infections acquired during pregnancy can cause abortions, stillbirths and mummification or resorption of the fetus (Dos Santos et al., 2016; Lopes et al., 2013). In sheep, congenital transmission is estimated to occur in 1–2% of animals (Innes et al., 2009; Bezerra et al., 2014). The consequences are influenced by the timing of the infection. Fetuses infected early in gestation are affected the most severely, and deaths are common. If the infection occurs between 50 and 120 days of pregnancy, it induces abortion, expulsion of mummified fetuses, or the birth of stillborn and weak lambs. Infections at mid-gestation are more likely to result in stillbirths or the birth of a weak lamb, often accompanied by a small mummified fetus. Congenitally infected lambs may be incoordinated, weak and unable to nurse. After 120 days of pregnancy, the infection generally leads to apparently normal lambs that can survive for a few days or grow normally and become protected against re-infections. Some animals may have signs of disseminated disease such as fever and dyspnea. Lambs infected late in gestation are less likely to be affected, and may be asymptomatic. Toxoplasmosis seems to be very rare or absent in cattle (Costa et al., 1977; Hosein et al., 2016), but fever, respiratory distress, nasal discharge and conjunctival hyperemia were described in experimentally infected calves. However, most infections including infections in non-pregnant small ruminants (Gazzonis et al., 2015), are subclinical. Outbreaks of congenital disease with abortions, stillbirths, mummified fetuses, neonatal mortality or systemic illness have been reported occasionally in pigs (Basso et al., 2015; Kim et al., 2009) with morbidity rates as high as 60% and mortality rates up to 10-42% in some fattening pigs (Wallander et al., 2016).

As in other species, toxoplasmosis in dogs can cause reproductive losses, (Arantes et al., 2009), sometimes with stillbirths and apparently healthy pups in the same litter (Bresciani et al., 2009). Generalized toxoplasmosis mainly occurs in young dogs (< 1 year). Common clinical signs include fever, tonsillitis, dyspnea, diarrhea and vomiting. Ocular affection is seldomly observed (Beckwith-Cohen et al., 2016). Liver or respiratory involvement can be rapidly fatal. Myocardial involvement is usually subclinical in young dogs, but arrhythmias and heart failure may be evident in some older animals (Calero-Bernal and Gennari, 2019). The vast majority of infections in domesticated cats are asymptomatic (Basso et al., 2015). Most cases of toxoplasmosis seem to occur in young or immunocompromised cats, although older animals, apparently immunocompetent have also been affected (Barrs et al., 2006; Nagel et al., 2013). The incubation period in animals is probably similar to the 5-23 day incubation period in humans. Experimentally infected kittens developed diarrhea 5-6 days after inoculation (Sato et al., 1993). Common early nonspecific clinical signs in acute toxoplasmosis include lethargy, persistent fever despite treatment with antibiotics and anorexia. Many cats develop respiratory signs including dyspnea. Severe respiratory involvement is often fatal. Some cats primarily have signs of an acute abdominal condition such as hepatitis (e.g., hepatomegaly, abdominal tenderness, diarrhea, occasional vomiting) or pancreatitis, or develop a nonspecific systemic illness. Self-limited diarrhea has been a component of some cases, and in rare instances, it may be accompanied by a palpable intestinal mass. Neurological signs may be prominent, especially in older

cats. The specific signs depend on the site(s) affected in the brain or spinal cord, and may include convulsions, changes in mentation (e.g., restlessness, somnolence, personality changes), hyperesthesia, incoordination, paralysis and depressed reflexes. Kittens with encephalitis may sleep excessively or cry constantly, and may have reddish, dark or pale retinal foci. In some cases, the retina is partially or completely detached (Lappin, 2010).

Toxoplasmosis in rabbits and poultry has not been well studied. Nevertheless, these two species represent a potential source of T. gondii infection (Dubey et al., 2010; Dubey, 2010). The only animal to which toxoplasmosis is fatal is the monk seal (Barbieri et al., 2016). These toxoplasmosis-caused deaths are detrimental because monk seals are one of the most endangered marine animals in the world (Carlson-Bremer et al., 2015). Toxoplasmosis is a significant cause of deaths among sea otters (Enhydra lutris nereis), which are often infected with an unusual genotype (Miller et al., 2008). Approximately 17% of sea otter deaths can be attributed to toxoplasma. While many believe fresh water runoff contaminated with cat feces is to blame, there is no definitive science on the source of infection (Jones and Dubey, 2010; Lindsay and Dubey, 2009). Some fish and marine mollusks may act as transport hosts. Anchovies, which are their primary food, can filter oocysts from the water. As anchovies are considered prey for practically every major predatory marine fish, mammal and bird, if the exposed anchovies harbor infectious oocysts, this could present a possible transmission path of T. gondii in the marine environment (Van de Velde et al., 2016). T. gondii DNA has been detected in captive snakes (Nasiri et al., 2016). Other animals reported to be affected fairly often include captive marsupials (Díaz-Ayala et al., 2016; Fernández-Aguilar et al., 2013; Hillman et al., 2015), New World primates (Cedillo-Peláez et al., 2011), and a number of cases have been reported in squirrels (Fayyad et al., 2016; Jokelainen et al., 2014). Rare clinical cases have been reported in many other species such as wild hares (Lepus europaeus, L. timidus) (Jokelainen, et al., 2013), a wild mink (Mustela vison), captive porcupines, a captive red panda (Ailurus fulgens fulgens), a captive giant panda (Ailuropoda melanoleuca) (Ma et al., 2015) and even captive fruit bats (Pteropus conspicillatus, P. scapulatus) (Cabral et al., 2013).

Birds can be intermediate hosts for T. gondii with asymptomatic infections documented in a number of species (Cooper et al., 2015). Clinical cases or outbreaks have been reported uncommonly in birds from multiple orders including Columbiformes (pigeons and doves) Passeriformes (passerine birds), Piciformes (woodpeckers) (Gerhold et al., 2007), Psittaciformes (parrots and other psittacines) (Ferreira et al., 2012), Galliformes (e.g., chickens, turkeys, guinea fowl), Sphenisciformes (captive black-footed penguins, Spheniscus demersus) and Apterygiformes (North Island brown kiwi, Apteryx mantelli) (da Silva et al., 2016). Birds with systemic toxoplasmosis often have few or no clinical signs before death, and any signs are frequently nonspecific (e.g., lethargy, anorexia, fluffed feathers). However, neurological signs were prominent in some birds, and others had respiratory signs (e.g., dyspnea) and/ or diarrhea. Affected birds often die very quickly. Chickens seem to be resistant to experimental infection by ingestion, but occasional clinical cases and outbreaks have been described in nature. Exposure is uncommon in pigs or chickens housed indoors, but is more common in outdoor pigs (seroprevalence of 10-50%) and free-range chickens (up to 100%). When diagnosed, toxoplasmosis in animals is treated by the same principles as in human medicine. Clinical cases are treated with antibiotics. Only certain drugs such as clindamycin, trimethoprim-sulfonamide, azithromycin and pyrimethamine, used alone or in various combinations, are effective. Corticosteroids may be administered concurrently in ocular disease to reduce inflammation. While antibiotics can suppress actively dividing parasites, they cannot destroy the tissue cysts, and are unlikely to completely eliminate T. gondii from the body. Intensive supportive treatment may be necessary in animals with disseminated disease.

Prevention

Felids are the only definitive hosts for T. gondii, and primary infection results in shedding of millions of unsporulated oocysts within a 2-week period on average (Opsteegh et al., 2015; Elmore et al., 2010). Oocysts become infectious within 1–5 days, depending on temperature and humidity (Jones and Dubey, 2010), and can be dispersed from defecation sites mechanically and transported to water by runoff (Beneson et al., 1982; Bowie et al., 1997). Infectious oocysts are very resistant to environmental conditions including freezing, and can survive up to 54 months in cold water, and up to 18 months after deposition in soil (Jones and Dubey, 2010). Unsporulated oocysts lose their ability to sporulate and become non-infectious if they are frozen for 7 days at −6°C (21°F), or heated for 1 day at 37°C (99°F) (Dubey, 1974). Sporulated oocysts are highly resistant to environmental conditions. Under laboratory conditions, they can remain infectious for more than a year in warm, moist soils, and for up to several years in cold (4°C) water. They are reported to survive freezing at −10°C (14°F) for nearly 4 months, or heating at 35°C (95°F) for 32 days. However, they do not survive well in arid, cool climates. Tissue cysts can remain infectious for weeks in body fluids at room temperature, and in meat for as long as the meat is edible and uncooked. Tachyzoites are more fragile, although they can survive in body fluids for a day, for as long as a week in goat milk, and up to 50 days in whole blood held at 4°C (39°F) (Kravetz and Federman, 2005). T. gondii oocysts are resistant to most disinfectants, but they can be inactivated by formalin and ammonia. They are destroyed rapidly by temperatures greater than 66°C (151°F), and can be killed with boiling water. Oocysts found in water can be eliminated by boiling or filtration (absolute 1 μm filter), but are resistant to chlorination. Tincture of iodine (2%) can inactivate T. gondii with a long exposure time of at least 3 hours. Some strains are more resistant than the others (Howe and Sibley, 1995).

Primary prevention includes several measures of feral and stray cat population control. Secondary prevention should be directed towards control of the possible contact with domesticated animals and humans with the possible sources of infection (Opsteegh, et al., 2015). Cat pets should be kept indoors, and not fed with raw meat, but with dry or canned food. Food sources should be removed to discourage the stray cats. Feral and stray cats, and pets who are allowed to roam outdoors may eat infected small mammals and spread the oocysts. Handling the stray cats, especially kittens should be avoided, and their adoption without proper veterinary surveillance should be discouraged. The garden sandboxes should be covered. During gardening, the gloves should be used and hands carefully washed afterwards. The litter box should be changed daily to remove potential eggs while still in non-infective stage. (Jones, et al., 2001). All the cutting boards, sinks, knives and other utensiles that might have been in contact with raw meat or unwashed fruits and vegetables shoud be thoroughly washed after the food preparation. The meat should be cooked at least at 150 C, or until it is no longer pink in the center, or until the juices run clear. Red meat that has been smoked, cured or frozen for at least 24 hours is also safe from this parasite. Tertiary level of prevention includes vaccination. A modified live vaccine is available for sheep in New Zealand and some European countries. The vaccine is a commercially produced live preparation for sheep (i.e TOXOVAX), which is a tissue culture grown S48 strain of T. gondii attenuated by over 8000 passages in mice (Frenkel et al., 1991). To this date, there is no humane vaccine against his parasite. Yet, there is a realistic hope of vaccine development in near future, in light of animal and human capability of acquiring good immunity against clinical toxoplasmosis subsequent to the postnatal infection.

Much of congenital toxoplasmosis can be prevented by educating women of childbearing age and pregnant women on the uttermost importance of the avoidance of raw or undercooked meat consumption and the possibilites of food cross-contamination (Carter et al., 1989; Foulon et al., 1988). Preventive strategies should aim to reduce prevalence of infection in meat, improve labelling of meat according to farming and processing methods, and improve the quality and consistency of health information given to pregnant women (Cook, et al., 2000). Studies of the unique environmental factors in various communities indicate that eating habitats and culture play an important role in transmission of this infection (Andiappan et al., 2014). Preventive measures should take into account the cultures and beliefs of people in various communities more than solving poverty and giving health education (da Silva et al., 2011).

In conclusion, toxoplasmosis presents a major health problem with a high socio-economic impact in terms of human suffering, the cost of caring for sick, mentally retarded and blind children (Guerina et al., 1994). It is a major cause of abortion and infertility in livestock, especially among ewes, and therefore significant cause of lost profitability in livestock and agriculture (Jones, et al., 2001). It is a major cause of morbidity in immunodeficient patients including AIDS (Atılla, 2015). T. gondii constitutes an important disease in modern world, especially in pregnant woman all around the globe.

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Toksoplazmoza: globalna zoonoza

Sažetak:

Toxoplasma gondii (T. gondii), obligatni intracelularni parazit koji je odavna poznat kao uzročnik kongenitalne toksoplazmoze kod ljudi, odnedavna je opet u žiži znanstvenog interesa zbog svojih nevjerojatnih bioloških svojstava. Iako je tradicionalno izučavan zbog svojeg zoonotskog potencijala, jer je njime kronično inficirana skoro trećina svjetske populacije, toksoplazma je od izuzetne važnosti i za veterinarsku medicinu, jer uzrokuje znatne gubitke u stočnom fondu, a kod nepažljivog rukovanja, njome se lako kontaminiraju živežne namirnice. Tradicionalno vezana uz transmisiju mačkama, danas je poznato kako je primarni izvor zaraze kod ljudi loše oprana svježa biljna hrana ili nedovoljno termički obrađeno meso. Novija istraživanja upućuju na sposobnost ovog parazita da modificira neurološki odgovor žrtve, čime se podržava njegova visoka infektivna sposobnost, a njegovo latentno postojanje u domaćinu dovodi se u vezu sa nizom neuroloških i psihijatrijskih stanja od afektivno-kognitivnih poremećaja, preko Parkinsonove i Alzheimerove bolesti do shizofrenije.

Ključne riječi: toksoplazmoza, trudnoća, urođene infekcije, mačka, zoonze