EPIDEMIOLOGICAL ASPECTS OF FELINE TOXOPLASMOSIS

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RESUMO: A toxoplasmose é uma zoonose de distribuição mundial, com grande importância na medicina humana e veterinária. Esta enfermidade é causada pelo *Toxoplasma gondii*, pode ser transmitida através da ingestão de cistos teciduais em carne infectada, a ingestão de alimentos ou água contaminados com oocistos e pela forma congênita, por taquizoítos que atravessam a placenta da mãe infectada para o feto. Os animais podem ser fonte direta ou indireta da infecção para o homem. Felinos em particular (hospedeiros intermediários ou definitivos para os parasitas) têm um papel importante na epidemiologia deste agente, como eles podem eliminar oocistos no ambiente doméstico. Portanto, a comunidade científica tem dedicado grandes esforços para avaliar a ocorrência de anticorpos de *Toxoplasma gondii* em felinos. O objetivo desta revisão é descrever as manifestações clínicas da toxoplasmose, para abordar o papel dos gatos na propagação da doença, bem como para discutir métodos de diagnóstico, medidas terapêuticas, a profilaxia e controle da doença.

Palavras-chave: taquizoíto; oocisto; zoonoses

ABSTRACT: Toxoplasmosis is a zoonosis distributed worldwide, which is of great importance in human and veterinary medicine. Toxoplasmosis, caused by *Toxoplasma gondii*, can be transmitted through the ingestion of tissue cysts in infected meat, ingestion of food or water contaminated with oocysts and congenitally, by tachyzoites crossing the placenta from the infected mother to the fetus. Felines in particular (intermediate or definitive hosts for the parasites) have an important role in the epidemiology of this agent, as they can eliminate oocysts in the domestic environment. The aim of this review is to describe clinical manifestations of toxoplasmosis, to address the role of cats in the spread of the disease, as well as to discuss methods of diagnosis, therapeutic measures, prophylaxis and control of this disease.

Key Words: tachyzoites; oocysts; zoonosis

INTRODUCTION

Felines (definitive hosts of *Toxoplasma gondii*) can eliminate fecal oocysts. These are highly infectious parasite forms that evolved to tolerate environmental adversities Cats defecate on soft earth or sand and bury their feces, which can remain in place for months. Cats generally do not present diarrhea during the period of oocysts excretion; hence, unless the cat is ill, little or no fecal residue is adhered to their perianal region. Because of its careful cleaning habits, fecal matter is not found in the pelage of clinically normal animals; therefore the possibility of transmission to humans by the act of touching or petting a cat is minimal or nonexistent. It is important to note that oocysts eliminated by cats, need to be in the extracorporeal environment for at least one day, under particular temperature and humidity conditions, to sporulate and become infective.

In this review we aim to provide information on the role of cats take in the cycle of this important zoonosis, suggesting guidelines to the community on how to best avoid human infections.

FELINE TOXOPLASMOSIS

The life cycle of *T. gondii* was first elucidated in the late 1960s/ early 1970s (Frenkel *et al.,* 1970; Hutchison *et al.,* 1968; Hutchison *et al.,* 1970; Hutchison *et al.,* 1971). These initial works demonstrated the shedding of infective Toxoplasma life forms by cats. Cats can act as definitive (Frenkel *et al.,* 1970) or intermediate host, sheltering the extra-intestinal parasite stages (Dubey, 2002; Dubey *et al.,* 1996).

T. gondii is transmitted via 3 primary routes: ingestion of tissue cysts, contamination through oocysts from infected cat feces, or congenital infection. In rare instances toxoplasmosis can also be transmitted through the ingestion of contaminated milk, transfer of body fluids or organ transplantation (Dubey, 1986; Miro *et al.,* 2004; Powell *et al.,* 2001).

Immunosuppression in cats with toxoplasmosis by concomitant infections with feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV), leads to a suppression of CD4 + and CD8 +, reduction in the expression of interleukins (IL-2, IL-6, TNF-ã), reactivation of latent disease and causes re-shedding of fecal oocysts (Akhtardanesh *et al.,* 2010; Lappin *et al.,* 1993; Sukhumavasi *et al.,* 2012; Swinger *et al.,* 2009; Tiao *et al.,* 2013). Types of feline of Toxoplasma

PATHOGENESIS AND DIAGNOSIS

Cats experimentally infected with *T. gondii* are often asymptomatic: few animals get sick and deaths due to Toxoplasma infection are rare (Omata *et al.,* 1990; Sato *et al.,* 1993). However, close scrutiny of a large number of cats diagnosed with toxoplasmosis (confirmed by histopathology), revealed lung infections (97.7%), neuropathy (96.4%), hepatitis (93.3%), pancreatitis (84.4%), cardiovascular (86.4%) and ophthalmic changes (81.5%) in most cats (Dubey and Carpenter, 1993).

Kittens infected during gestation (via the placenta) or through the milk of infected queens can undergo inflammatory processes that affect the liver, lungs and central nervous system. These are clinically displayed as uveitis, lethargy, depression, ascites, encephalitis, hypothermia and sudden death. Experimental infection of pregnant cats with the parasite leads to abortion and high neonatal mortality (Dubey and Hoover, 1977; Dubey *et al.,* 1977; Dubey *et al.,* 1996; Powell *et al.,* 2001; Sakamoto *et al.,* 2009; Sato *et al.,* 1993). In adults with primary or recurrent

infection, clinical symptoms are anorexia, lethargy, dyspnea, pneumonia, intermittent fever, emaciation, vomiting, diarrhea, hyperesthesia, stiff gait, lameness, neurological deficits, dermatitis and death (Dubey and Lappin, 2006). Furthermore, *T. gondii* infections can cause jaundice, cholangitis, ascites, hepatitis and pancreatitis (leading to hepato-biliary compromise) (Harvey and Greeffydd-Jones, 2009; Smart *et al.,* 1973). Under conditions of pancreatitis, there is elevation of serum amylase and lipase as well as reduction in serum calcium (Dubey and Lappin, 2006). Toxoplasmosis can cause tissue impairment, leading to hypo-proteinemia, hypo-globulinemia, and increased serum enzymatic activities of alanine transaminase (ALT), alkaline phosphatase (ALP), bilirubin and hyper-gammaglobulinemia (Dubey and Lappin, 2006).

In the acute stage of the disease, radiographic examination of the thorax of affected animals can generally detect a diffuse interstitial alveolar pattern with lobar distribution. In severely compromised animals, it is possible to observe a diffuse and homogeneous pattern due to alveolar coalescence. Abdominal radiography of animals severely affected by toxoplasmosis show intestinal masses, increased mesenteric lymph nodes and ascites; whereas ultrasonography frequently show tissue or organ enlargement, suggestive of granuloma formation. Tomography and magnetic resonance imaging are further techniques that can be employed in the clinical to detect damages to the central nervous system of infected animals (Dubey and Lappin, 2006).

Toxoplasmosis can also lead to ocular symptoms, caused by parasite invasion of the uveal tract, retina and optic nerve, triggering inflammation with exudative retinal displacement, iridocyclitis, iritis, chorioretinitis, aqueous flare, keratic precipitates, crystalline lens dislocation and glaucoma (Dubey and Lappin, 2006). Ocular symptoms can occur in cats with or without systemic infections. The principal symptoms of acute toxoplasmosis are non-regenerative anemia, leukocytosis with neutrophilia or lymphocytosis, monocytosis and eosinophilia (Dubey and Lappin, 2006). Necropsy of animals which succumbed to toxoplasmosis frequently show severe abnormalities in the central nervous system such as: cerebral necrosis, discoloration of nervous tissue, cerebellar necrosis, atrophy, encephalitis, non-suppurative menigo-encephalomyelitis and gliosis, with eventual compromise of peripheral nerves. Necropsy can also show: pulmonary necrosis, hepatic and mesenteric lymph node necrosis (Dubey and Lappin, 1998). However, the unambiguous confirmation of the diagnosis depends on the isolation of the parasite and positive serodiagnosis (Lapppin, 2004; Carvalho, 2007).

Once infected, animals frequently shelter bradyzoites in their tissues, which encourages a long-term humoral immune response. This allows the detection of antibodies against *T. gondii* by indirect immunofluorescence as well as by direct agglutination test, hemagglutination test and enzyme immunoassay, in diagnosis and epidemiological survey of this zoonosis (Dubey and Lappin, 2006; Zhang, *et al.,* 2000).

Anfray *et al.,* (2005) described a positive diagnosis of *T. gondii* infection in a female cat, by employing immunohistochemistry and polymerase chain reaction (PCR) on samples prepared from cutaneous nodules. Park and colleagues (Park *et al.,* 2007) described histopathologic and molecular characterization of *T. gondii* infections from samples collected from a mammary gland nodule. The cytological examination of this sample showed

pyogranulomatous, necrotizing panniculitis, vasculitis and mastitis with clusters of tachyzoites, confirming of the diagnosis by molecular techniques.

Dubey and Powell, (2012) reported the occurrence of six million *T. gondii* oocysts in a fecal sample from a 6-year-old male cat with clinical toxoplasmosis symptoms (lethargy, anorexia, fever and diarrhea) and with positive serology for *T. gondii* (1:800 by the modified agglutination test). The authors further genotyped the parasites reporting, for the first time, a type I infection in the United States of America (USA).

The occurrence of fecal *T. gondii* oocysts is low as they are released for only one to two weeks during the initial stages of the disease. One method to facilitate the detection of oocysts in the feces of cats and hence provide a parasitological diagnosis is the Sheather method (centrifugal-flotation in sucrose). However, microscopic examination of samples prepared using this method is unable to morphologically distinguish oocysts from the evolutionarily conserved *T. gondii*, Sarcocystis, Frenkelia and Besnoitia. This discrimination can only be achieved by molecular techniques (Dubey and Lappin, 2006).

T. gondii tachyzoites, life form responsible for multiplying the population of parasites in the host, can be detected by cytology of body tissues and fluids samples, such as blood, cerebrospinal fluid, peritoneum and bronchoalveolar lavage samples. The tachyzoites may also be isolated from samples of ascitic fluid or pleural effusion (Brownlee and Sellon, 2001; Dubey and Lappin, 2006).

EPIDEMIOLOGY OF FELINE TOXOPLASMOSIS

Multiple research groups have performed epidemiological studies of feline Toxoplasmosis. In Table 1 we summarize some of the epidemiological studies performed over the last 15 years, with special emphasis to infections on Brazil.

Table 1 - Occurrence of *Toxoplasma gondii* infection in cats, in the period from 1999 to 2004, in different countries.

Locality	Seroprevalence (%)	Method*	Reference
Brazil	73.0	IFAT	Garcia et al. (1999)
Brazil	46.0	IFAT - IgG	Carvalho (1999)
	43.4	IFAT - IgM	
Brazil	19.4	IFAT	Langoni et al. (2001)
Brazil	26.3	MAT	(Silva et al., 2002)
Brazil	84.4	MAT	(Dubey, 2004)
Brazil	35.4	MAT	Pena et al. (2004)
Brazil	17.0	Indirect Hemagglutination	(Meireles et al., 2004)
	40.0	ELISA	
Australia	39.0	ELISA	(Sumner and Ackland, 1999)
United States	42.0	MAT	(DeFeo et al., 2002)
United States	48.0	MAT	Dubey et al (2002)
Belgium	70.2	Aglutinação Direta	(Dorny et al., 2002)
Spain	45.0	MAT	(Gauss et al., 2003)
Spain	32.3	IFAT	(Miro et al., 2004)
Brazil	25.0	IFAT	(Bresciani et al., 2007)
Brazil	16.3	IFAT	(Cruz Mde et al., 2011)
Brazil	50.6	IFAT	(Braga Mde et al., 2012)

*IFAT: Indirect Fluorescent Antibody Test; ELISA: Enzyme Linked Immunosorbent Assay; MAT: Modified Agglutination Test.

Dubey *et al.* (2004), isolated 37 *T. gondii* samples from 54 domestic cats from Paraná, in the city of Santa Isabel do Ivaí, during an outbreak of human toxoplasmosis. Most of these isolates, 15 of which were of type I and 22 of type III, were virulent in mice, however, there was no correlation between the tested genotype and virulence.

In the same year, Pena *et al.* (2004) isolated 47 samples of *T. gondii* from 71 cats in São Paulo, finding that 72.4% of the animals were infected with type I, 25.5% were infected with type III and 2.1% had mixed infection (types I and III). In contrast to the work reported by Dubey (2004), Pena *et al.*, (2004) showed that in mice, Type I parasites had a significantly higher virulence (97% mortality) than type III (42% mortality).

Bresciani *et al.* (2007) conducted studies to investigate the presence of antibodies against *T. gondii* in cats from the northwestern region of the state of São Paulo, and observed a higher incidence of *T. gondii* antibodies with aging (probably due to the cumulative exposure to the parasites).

Coelho *et al.* (2011) also performed epidemiological studies of cats infected

with *T. gondii* and found a strong correlation between disease incidence and factors such as: postnatal infection, diet and presence of rodents in the environment. Sobrinho *et al.* (2012) investigated concomitant infections with Toxoplasma and Leishmania and found no correlation between the occurrences of either parasite.

TREATMENT AND PROFILAXIS

Clindamycin hydrochloride, administered orally or parenterally, is effective in the treatment of systemic toxoplasmosis and can reduce the elimination of oocysts by cats. It is used toxoplasmosis treatment in animals and humans, and indicated for the treatment of pregnant queens. This drug has good intestinal absorption, is transported through the blood brain barrier and leads to clinical improvement of affected animals within 24 to 48 hours from the onset of treatment. In this time frame, it is possible to observe a return of appetite and normalization of the body temperature. With further treatment, after weeks there are reports of re-establishment of the operation of cranial and spinal nerves, as well as the resolution of polymyositis. Clinical improvement of ocular damage is also described after a week of treatment with clindamycin hydrochloride. However, excessive doses may cause local irritation in the digestive system, with side effects such as anorexia, vomiting and diarrhea (LAPPIN, 2004; (Dubey and Lappin, 2006; Swinger *et al.*, 2009)). Glucocorticoids are generally contraindicated in the treatment of *T. gondii* infections, since this class of compounds can exacerbate the systemic symptoms of the disease. However, this class of compounds can be advised for the topical treatment (in combination with clindamycin chloride) of ocular lesions (Dubey and Lappin, 2006; Harvey and Greeffydd-Jones,

2009). Clindamycin treatment can also be combined with folic acid supplementation in cases where there is bone marrow compromised by the infection (Dubey and Lappin, 2006). Trimethoprim-sulfametaxol combination therapy is also effective on the treatment of toxoplasmosis, in particular on the treatment of ocular lesions in human (Dubey and Lappin, 2006). In addition to trimethoprim-sulfametaxol, sulfadiazine-trimethoprim combination therapy is also recommended for the control of toxoplasmosis in small animals (Papich, 2009). Barbosa *et al.*(2012) studied the in vitro and in vivo activity of enrofloxacin in the treatment of toxoplasmosis, demonstrated its effectiveness and low toxicity. Enroflacin can therefore become an alternative treatment against toxoplasmosis.

A simple recommended method to minimize the risk of contamination of cats and humans by Toxoplasma is to discard cat stools daily, as oocysts require at least 24 hours to sporulate and become infectious. It is also important to minimize opportunities for coprophagia by animals, as well as the control of insects and rodents in the environment. Furthermore, neither humans nor cats should consume raw or undercooked meat or raw milk, and care should be taken to ensure the consumption of clean fruit and vegetable and suitably treated water (Monteiro, 2010).

CONCLUSION

Toxoplasmosis it is a zoonosis of worldwide distribution that causes a range of clinical symptoms, from the absence of any obvious abnormality, to death of the infected host. Thus, diagnosis, treatment and control of toxoplasmosis present a great challenge to the veterinary in a feline clinic.

Although is possible for *T. gondii* to survive and multiply in the absence of cats, evidence gathered so far indicates that this host is of pivotal importance in the transmission of toxoplasmosis worldwide. Thus, the veterinarian plays a vital role in the control of this disease.

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