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Maternal and congenital toxoplasmosis, currently available and novel therapies in horizon

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Over one billion people worldwide are predicted to harbor *Toxoplasma* infection frequently with unknown lifelong health consequences. Toxoplasmosis is an important cause of foodborne, inflammatory illnesses, as well as congenital abnormalities. Ubiquitous *Toxoplasma* has a unique tropism for central nervous system with a mind-bugging effect and is transmitted sexually through semen. Currently available therapies are ineffective for persistent chronic disease and congenital toxoplasmosis or have severe side effects which may result in life-threatening complications. There is an urgent need for safe and effective therapies to eliminate or treat this cosmopolitan infectious and inflammatory disease. This investigation discusses pathogenesis of maternal and congenital toxoplasmosis, the currently available therapies in practice, and the experimental therapeutic modalities for promising future trials.

**Keywords:** fetal maternal, congenital toxoplasmosis, mind alteration, sexual transmission, atovaquone, diclazuril

**INTRODUCTION**

Over one billion people worldwide are predicted to harbor *Toxoplasma* infection frequently with unknown lifelong health consequences. Toxoplasmosis is one of the most important foodborne inflammatory illnesses, as well as congenital abnormalities (Hoffmann et al., 2012). *Toxoplasma* is classified as “Category B pathogen” which once infected, the organisms dwell in organs such as muscles and brain in cyst forms for the life of the patient/host to become reactivated. The organisms have a sexual stage in cat’s intestinal epithelial cells which form resistant oocysts passed in feces and matured in dirt (Figure 1). Humans and other animals develop systemic infection in asexual form by ingestion of contaminated vegetable, fruits, water, or consumption of infected milk and undercooked sea food, poultry, and livestock. Tachyzoites infect nucleated host cells and utilize monocytes, macrophages, and dendritic cells as “Trojan Horse” (1) to escape the host immune defense (Elsheikha and Khan, 2010), (2) to bypass the blood–brain barrier (Bierly et al., 2008) and the placenta barricade, and (3) to spread and form systemic disease. *Toxoplasma* infects particularly rural and impoverish communities of women, African American, Hispanics, and Native Americans as a “frequently ignored disease of poverty” (Hotez, 2008). Toxoplasmosis is considered as the second major cause of foodborne death in the United States (Scallan et al., 2011). The *Toxoplasma* annual cost of illnesses is about $3 billion and the quality-adjusted life loss is equal to 11,000 years in the United States (Hoffmann et al., 2012). Toxoplasmosis in immune-intact individuals is generally symptomless and undetected or appears like flu syndrome and malaise. However, it can cause severe pathological consequences in immunocompromised patients, fetuses, and neonates and lead to demise and death (Dubey and Jones, 2008).

**MATERNAL CONGENITAL TOXOPLASMOsis**

The importance of maternal and congenital transmission has long been recognized since 1939; when a neonate from New York developed toxoplasmosis (Wolf et al., 1939; Jones et al., 2001). During progression of pregnancy, maternal immune system confronts a dual predicament: the growing embryo, and the environmental toxins and pathogens threatening mom and fetus. In fact, successful pregnancy involves an elegant equilibrium in organizing the immune system at the fetal-maternal and uterine milieu resulting in tolerance (TH2) of the fetus (Norwitz et al., 2001; Muzzio et al., 2014) and defense (TH1) against the pathogenic agents. Women who have acute or reactivated toxoplasmosis during pregnancy can transplacentally transmit organisms to their fetus. As, tachyzoites bypass the placental blood barrier and invade the fetal organs to propagate and compromise the embryonic developmental process. About 50–80% of child-bearing Brazilian women and 50% of children have anti-*Toxoplasma* antibodies. Also, 5–23 neonates are found to be infected per 10,000 in Brazil (Dubey et al., 2012).

Congenital toxoplasmosis can manifest with severe complications, such as miscarriage, fetal developmental retardation, encephalitis, neurological, mental illnesses, visual, and auditory inflammatory disorders, cardiovascular abnormalities, and pains (Dunn et al., 1999; Gilbert and Gras, 2003; Gras et al., 2005; McLeod et al., 2006; Remington et al., 2006; Oz and Tobin, 2012). The severity of complications relies on the gestation period, as the early infection shows more severe outcomes (Dunn et al., 1999; Remington et al., 2006). While, fetuses infected in late gestation are born normal, may develop central nervous system (CNS) symptoms and retinchorioiditis later in life. Also, the new lesions may occur in untreated as well as treated children (Dunn et al., 1999).

A predominant source of infection in North America is contaminated food and water with oocysts passed in the cat’s (definite host) feces (Boyer et al., 2011). Sera and surveys from 76 moms with congenital infected newborns were collected from four different epidemic areas and investigated by the National collaborative Chicago-based congenital toxoplasmosis. The data revealed 78%
of the moms acquired primary infection from oocysts form, while only 49% had direct contact with house cats. Hence, extensive educational hygienic programs, effective cats’ infection prevention, and vaccination plans, along with serological testing of pregnant women and newborns, followed by the treatments are needed to prevent maternal congenital toxoplasmosis (Boyer et al., 2011).

MATERNAL REACTIVATION AND CONGENITAL TOXOPLASMOsis

Toxoplasmosis reactivation is a major concern in pregnant, immunodeficient, blood transfusion, bone marrow, and organ transplant patients, when the protective cyst’s wall ruptures and organisms reach the lymphatic and blood cells to activate and propagate the infection. Maternal congenital toxoplasmosis is instigated by the transplacental transmission of organisms in maternal infection (Buxton et al., 1991), as Toxoplasma organisms alter balance in immune milieu leading to inflammatory response. A low number of Toxoplasma organisms can induce an extensive inflammatory and immune reaction as shown in the murine model of fetomaternal toxoplasmosis (Oz and Tobin, 2012). Therefore, taming exaggerated inflammatory response in fetal–maternal toxoplasmosis is necessary to prevent severe tissue destruction and fatality during the pathogenic clearance.

According to Massachusetts Department of Health, about 1 case of congenital toxoplasmosis occurs for every 10,000 live births. It is estimated that from 4,000,000 live births each year in the United States, 400 have acquired congenital toxoplasmosis (Mead et al., 1999). This rate is extensively higher for other developing countries. For instance, retrospective trials from Argentina (2000–2011) reviled 18% (2206/12035) prevalence rate of anti-Toxoplasma antibody in pregnant women. Thirty eight per 10,000 of these moms had developed acute infection and 5.8% transplacentally infected their neonates (Carral et al., 2013).

TOXOPLASMA MIND-BUGGING SEXUAL ATTRACTION AND MENTAL DISORDERS

Recent investigations reveal that Toxoplasma provokes a brain and mind alteration with sexual arousal in rats seeking cat, while uninfected normal rats fear and avoid predator’s urine odor with an immediate, innate survival defensive behavior (House et al., 2011; Knight, 2013). Therefore, the brain impaired and fearless infected rodents are eaten up by feline to fulfill the organism’s sexual propagation in definitive host “cat”. Toxoplasma manipulates the limbic brain neurons responsible for instinct defensive response and augments activity in adjacent limbic regions of sexual desire when exposed to cat’s urine odor (House et al., 2011).

Toxoplasmosis is a sexually communicable disease as organisms are transmitted by contaminated semen during natural mating. Also, artificial insemination with contaminated semen can infect animals with vertical transmission with 80% embryonic disruption (Arantes et al., 2009; Lopes et al., 2013; Wanderley et al., 2013). Indeed, there exists a potential sexual transmission route with infected semen during mating as well as artificial insemination with subsequent vertical transmission to the progeny in humans.

Toxoplasma has strong tropism for the CNS with adverse affect in the brain neuro-structural development and pathological as well as psycho-behavioral impairment and mental challenges (Bachmann et al., 2005; Brown et al., 2005; Wang et al., 2006). Maternal Toxoplasma infection has been related
with risk for schizophrenic events and autism with over 40 supporting investigations for the incidence of *Toxoplasma* infection among these patients (Fleg, 2013). *Toxoplasma* infection may evolve brain dopamine dysregulation (Torrey et al., 2007; Fekadu et al., 2010). Longitudinal and cross-sectional trials in seropositive females with chronic toxoplasmosis have shown high risk of self-harm, accidents and non-fatal suicidal aggression than in seronegative individuals (Pedersen et al., 2012; Zhang et al., 2012).

Pregnant women with latent infection have a higher risk of infants with genetic or developmental disorders such as premature and postnatal slow motor development due to infection provoked immunosuppression in moms. Some of these defects are related to malnutrition caused by diarrhea and gut disorders or directly congenital toxoplasmosis induced cognitive and developmental deficits (Kankova et al., 2012).

**AUTOIMMUNE DISEASE AND TOXOPLASMOsis**

Ubiquitous *Toxoplasma* infection is indicated to provoke series of chronic inflammatory and autoimmune disorders. Immunosuppressants and monoclonal antibodies such as anti-TNF which are widely used in healthcare for the treatment of autoimmune diseases, and organ transplantation may result in acute toxoplasmosis in these patients. However, the nature of this interaction and mechanism between the development of acute toxoplasmosis and immunosuppressant therapies are still being investigated. In a clinical trial, sera of 1514 patients with *Toxoplasma* and immunosuppressant therapies are still being interaction and mechanism between the development of acute toxoplasmosis in these patients. However, the nature of this interaction and mechanism between the development of acute toxoplasmosis and immunosuppressant therapies are still being investigated.

Pregnant women with latent infection have a higher risk of infants with genetic or developmental disorders such as premature and postnatal slow motor development due to infection provoked immunosuppression in moms. Some of these defects are related to malnutrition caused by diarrhea and gut disorders or directly congenital toxoplasmosis induced cognitive and developmental deficits (Kankova et al., 2012).

**DIAGNOSIS OF MATERNAL CONGENITAL TOXOPLASMOSIS**

Maternal *Toxoplasma* infection as a serious risk factor for the fetus requires accurate and urgent diagnosis for possible prevention and treatments. Maternal congenital toxoplasmosis is commonly diagnosed with utilizing repeated serological tests to assess the types and the levels of anti-*Toxoplasma* antibodies. Pregnant moms are required to be tested in Austria, France, Italy, Portugal, and Uruguay for antibody detections, but a limited screening program is used in Belgium, Germany, and Switzerland. Congenital and neonatal screening for toxoplasmosis is performed in over two million women and their babies each year in Europe, North and South America with estimated cost of over 500 million dollars (Petersen and Schmidt, 2003). While, the United States does not require routine screening, it is recommended that infants with serious systemic complications to be tested for toxoplasmosis (Armstrong et al., 2004). In addition, seronegative pregnant women indicating no previous exposure to infection are at risk for the infection and recommended to be serology tested monthly until the labor.

Diagnosis of toxoplasmosis is based on the presence of IgM and IgG anti-*Toxoplasma* antibodies, and molecular techniques to detect organisms (Teixeira et al., 2013). Acute infection is associated with high levels of anti-*Toxoplasma* IgM antibody followed by a rise in IgG levels in 1–3 weeks. Detection of IgM or elevation of IgG anti-*Toxoplasma* antibodies suggests acute or reactivation with a possible transmission of infection to the fetus. An amniotic fluid test is required to confirm fetal health status and possible exposure to the maternal infection.

Sabin-Feldman dye test “the international gold standard” is a complement-lysis-based assay and relatively sensitive and specific for anti-*Toxoplasma* IgG antibody. The test is considered more reliable than available ELISA kits, but requires live organisms treated with each diluted serum analyzed under the microscope (Dando et al., 2001).

In infants with neurological disorders, anti-*Toxoplasma* IgM and IgA antibodies plus cerebrospinal fluid PCR to detect *Toxoplasma* DNA are considered to provide a high sensitivity for diagnosis of congenital toxoplasmosis (Olariu et al., 2014). CSF-PCR was positive in 47% of about 60 infants from infected moms, while 0% positive in uninfected healthy ones.

Additionally, western blot analysis is used to detect IgM and IgA (di Carlo et al., 2011) and RT-PCR for DNA in amniotic fluid with 98% sensitivity and 100% specificity (Teixeira et al., 2013).
Atovaquone, a hydroxy-1,4-naphthoquinone and FDA approved, has a half-life of 1.5–3 days and mainly binds to plasma proteins (99%) and is excreted into feces (94%) without being metabolized (Rolan et al., 1997). Atovaquone has been shown to protect against maternal congenital toxoplasmosis and inflammatory complications in murine model (Oz and Tobin, 2012). Atovaquone was superior than the standard of care with combined pyrimethamine plus sulfadiazine or pyrimethamine plus clindamycin therapies against brain inflammatory responses in murine (Oz and Tobin, 2012), diclazuril was superior than atovaquone in improving anemia, colonic length, and hepatic complications against maternal toxoplasmosis (Oz and Tobin, 2014). In addition, diclazuril and atovaquone combination therapy is anticipated to exert a unique synergistic effect against toxoplasmosis. Diclazuril monotherapy or combination with atovaquone therapy may warrant clinical trials in maternal congenital toxoplasmosis as well as in ocular and chronic toxoplasmosis. Finally, diclazuril is anticipated to be used as a novel protective and preventive measure to eliminate the cycle of Toxoplasma infection in the definitive host, feline.

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