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Fetomaternal and Pediatric Toxoplasmosis

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Abstract

Toxoplasmosis is one of the most important causes of foodborne illnesses and inflammatory complications, as well as congenital disorders. Promiscuous *Toxoplasma* is transmitted by contaminated food and animal produce, water, vegetations, fruits and sexually through semen. *Toxoplasma* infects nucleated cells with a unique tropism for muscles and central nervous system and a mind bugging malicious effect. Pregnant women with acute or reactivated toxoplasmosis can transmit *Toxoplasma* via transplacental to the fetus. The severity of congenital toxoplasmosis depends on the gestation period, as infection in early pregnancy causes more severe consequences. Congenital toxoplasmosis complications include miscarriage, encephalitis, neurological retardation, mental illnesses, auditory and visual inflammatory disorders, cardiovascular abnormalities, and pains. Current therapies are inefficient for congenital and chronic toxoplasmosis or have severe side effects with life threatening complications. There is an urgent need for effective and safe therapeutic modalities to treat complications of toxoplasmosis and effective vaccines to eliminate the infectious agent. This investigation will discuss pathogenesis of feto-maternal, congenital and pediatric toxoplasmosis, the current available therapies in practice, and explore those therapeutic modalities in experimental stages for promising future trials.

Keywords

Toxoplasma; fetal maternal; congenital; pediatric toxoplasmosis mind alteration; sexual transmission

Introduction

About 1.5 billion people are globally infected with *Toxoplasma* frequently with lifelong health consequences.[1,2] Toxoplasmosis is one of the most important foodborne inflammatory illnesses, and fetal and pediatric abnormalities.[1,2] *Toxoplasma* is a “Category B pathogenic agent according the Center for Disease Control (CDC) and National Institute of Health (NIH). When the host is infected, the organisms mainly reside in muscles and brain in cyst forms for the lifelong awaits reactivation. Toxoplasmosis in normal immune intact individuals is usually undetected and appears like flu syndrome and malaise. However, it causes severe pathophysiological complications in immune-compromised patients, fetal, neonatal and pediatrics leading to demise and mortality.[3]

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The organisms have an asexual stage in every animals and humans to develop cysts. The sexual stage exclusively occurs in cat's intestinal epithelial cells which forms resistant immature unsporulated oocysts which pass in feces and mature in dirt. Humans and animals develop systemic infection in asexual form after ingesting contaminated water, vegetable, fruits, 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 shuttle "Trojan Horse" to a) evade the immune defense,[4] b) invade the blood brain barrier[5] and evade the placenta cordon c) and develop systemic disease. *Toxoplasma* is the 2nd major infectious agent to cause foodborne hospitalization and death in the United States.[6] *Toxoplasmosis* is known as a disease of impoverish and rural areas and common in children, and women.[7] The annual cost of toxoplasmosis illnesses is estimated $3 billion and further the quality-adjusted life loss is equal to 11,000 years in United States alone.[1]

Toxoplasma was discovered over a century ago (1908) by Nicolle and Manceaux in an African rodent. *Toxoplasma* infection is one of the most important sources of foodborne, feto-maternal, congenital and pediatric infectious diseases. Following acute phase, the organisms dwell mainly in muscles and brain in cyst forms for the lifelong awaiting to be reactivated. The importance of feto-maternal and congenital transmission was recognized in 1939; when a newborn baby boy from New York developed severe systemic symptoms and shortly after died of unknown complications. *Toxoplasma* organisms were discovered in pathology and the disease was called congenital toxoplasmosis.[8,9] Regardless of ongoing investigations, there is no safe and effective therapy for congenital, chronic infection or a vaccine available to prevent toxoplasmosis.

Transmission

The common routes of transmission include:

- **a.** Foodborne through contaminated fruits and vegetables, water, milk, meat, unwashed or utensils.
- **b.** Feto-maternal (congenital).
- **c.** Cat and man by handling contaminated water and soil or accidental fecal-oral infection.
- **d.** Contaminated blood and organ transplant transmission.
- **e.** Sexual Transmission by contaminated semen, and body fluid.
- **f.** Accidental laboratory acquired infection by inoculation of contaminated material.
- **g.** Contaminated milk with cysts and tachyzoites or environmental contamination of udders with oocysts and by breast feed babies from actively infected mother.

Toxoplasma is not transmitted by direct contact through intact skin or airborne. *Toxoplasma* tachyzoites are released into milk and contaminated milk can transmit infection when consumed raw and unpasteurized milk from livestock, camels and donkeys' milk.[3,10,11,12] Tachyzoites can survive in the refrigerated raw milk and milk products for several days and

transmit the infection. Overall, feto-maternal (congenital) transmission can pose the highest risk and the most devastating pathological injuries to fetus and neonates.

Maternal Congenital Toxoplasmosis

Pregnancy is a state of tolerance to bear the development of fetus in maternal uterus. During the succession of pregnancy, the maternal immune system faces a complex dilemma to protect the growing embryo, and to fight back the environmental toxins and pathogens which are threatening the mother and her fetus. Indeed, a complete pregnancy requires a fine balance in coordinating the immune system at the fetal-maternal and uteri milieu resulting in tolerance (TH2) of the [fetus13,14] and defense (TH1) against the pathogenic agents. Pregnant women with acute or reactivated toxoplasmosis can transmit *Toxoplasma* via transplacental to the fetus. Organisms breakdown the placental blood barrier and propagate in the fetal organs and compromise the embryonic developmental process. In Brazil, 5 to 23 neonates per 10,000 are reported to have *Toxoplasmosis*. Also, 50–80% of the pregnant women and 50% of children there have *Toxoplasma* antibodies.[15]

The severity of congenital Toxoplasmosis depends on the gestation period, as infection in early pregnancy causes more severe consequences.[16,17] The fetuses infected during late pregnancy may be born normal, but can show CNS symptoms and retinochorditis later in developmental stages. Also, the new lesions may occur in untreated as well as treated children.[16]

Congenital toxoplasmosis complications include miscarriage, encephalitis, neurological retardation, mental illnesses, auditory and visual inflammatory disorders, cardiovascular abnormalities, and pains.[2,16–20] A predominant source of infection in North America is contaminated food and water with oocysts passed in the cat's (definite host) feces.[21] Surveillance and blood samples were collected from mothers with *Toxoplasma* infected neonates from 4 different locations by the National collaborative Chicago-based congenital toxoplasmosis. The investigation showed 78% (76) of moms had become infected by exposure to oocysts yet only 49% of these women had house cats. Therefore, restrictive preventive measures are required to protect moms' exposure and congenital toxoplasmosis. These include hygienic educational programs, development of effective vaccination programs to prevent cats from infection along with serological examination of women during pregnancy and their newborns, following treatment of infected moms and babies.[21]

Congenital and Pediatric Toxoplasmosis and Maternal Reactivation

In the United States ~4,000,000 live births each year 400 are borne with congenital toxoplasmosis.[22] Massachusetts Department of Health estimates one case of congenital toxoplasmosis to occur for every 10,000 live births. Indeed, the prevalence rate of infection is extensively higher in developing countries. In a retrospective trial from Argentina (2000–2011) 2206 from 12035 pregnant women (18%) tested were positive for anti-*Toxoplasma* antibody. In addition, 38 per 10,000 of these moms had acute infection and 5.8% transplacentally infected their babies before birth.[23]

Toxoplasmosis reactivation is a major source of trepidation in pregnancy, blood transfusion, bone marrow and organ transplantation, AIDS and in immunodeficient patients. It occurs when an old shielded infection becomes activated and organisms (tachyzoites) are released from cysts to attack blood (*e.g.* neutrophils, macrophages) and lymphatic cells and infect other organs. In pregnant moms organisms bypass placental barrier and infect fetus.[24] *Toxoplasma* manipulates the immune system leading to exaggerated inflammatory reaction. As a few organisms can trigger a strong immune and inflammatory response and organ damage as is demonstrated in an experimental model for toxoplasmosis in pregnant mice.[1,25] Severe immune and inflammatory response creates additional challenging matters specifically during fetal and congenital toxoplasmosis which compromises organs formation and developmental stages. Therefore, taming exaggerated inflammatory response in fetal-maternal toxoplasmosis is necessary to prevent severe tissue destruction and fatality during the pathogenic clearance.

Toxoplasma Mental Disorders and Mind Bugging Sexual Attraction

Toxoplasma organisms have tropism for CNS and neurons and cause encephalomyelitis and other severe complications in children and immunosuppressed patients. *Toxoplasma* manipulates the limbic brain neurons responsible for instinct defensive response and modulates activity in adjacent limbic regions of sexual desire.[26] Recent investigations reveal that *Toxoplasma* provokes a brain and mind alteration. Uninfected normal rodents freight to avoid predator with an immediate innate survival defensive behavior.[26,27] In contrast, *Toxoplasma* infected rodents with impaired brain and altered mind become mesmerized by the feline's smell which daringly follow until eaten up to complete the sexual development of organisms in cat the "ultimate host"[26].

Toxoplasmosis is a sexually transmissible disease as organisms are spread by contaminated semen during natural mating. Also, synthetic insemination with *Toxoplasma* contaminated semen can infect animals with vertical transmission to cause 80% embryonic disruption.[28–30] There is a potential for sexual transmission route with infected semen during mating as well as artificial insemination with subsequent vertical transmission of infection during progeny in humans.

Toxoplasma shows attraction toward the central nervous system and affects the brain neuronal composition and causes pathological as well as psychological and behavioral disorders and mental complications.[31–33] Maternal *Toxoplasma* infection has been linked with risk for autism and schizophrenia with extensive supporting investigations for the incidence of *Toxoplasma* infection amongst these patients.[34] *Toxoplasmosis* affects brain and causes dopamine dysregulation.[35,36] Longitudinal and cross sectional trials demonstrate seropositive women to have a high risk of self-harm, accidents and nonfatal suicidal aggression than in seronegative individuals.[37,38]

Those women with dormant infection are in a higher jeopardy when become immunosuppressed to have congenitally infected babies with genetic or developmental disorders. These include postnatal slow mental and motor development provoked by mom's infection. Some of these defects are caused by congenital infection or indirectly stemmed

from malnourishment, diarrhea and gut disorders to induce mild to severe cognitive and developmental deficits.[39] In contrast, some investigations deny link between *Toxoplasma* IgG seropositives and mental disorders. In a trial using Patient Health Questionnaire Survey data collected by National Health and Nutrition Examination (2009–2012) no association was reported between *Toxoplasma* seropositives (13%) and incidence of depression (8%) or suicidal thoughts in the subjects.[40]

Toxoplasmosis and Autoimmune Disease

Etiological factors in the induction of autoimmune diseases remain ambiguous yet may exist a possible association with toxoplasmosis. For instance, the use of immunosuppressants, and biologicals (e.g., monoclonal antibodies; as anti-TNF) are common in the treatment of autoimmune diseases and organ transplantation which may provoke activation of toxoplasmosis in patients. However, the nature, mechanism and the link between acute toxoplasmosis and immunosuppressant therapies are still being investigated. In a multicenter clinical trial sera of patients (1514) with 10 different autoimmune diseases and controls (437) from Latin America and Europe were investigated for the prevalence of auto-antibodies and anti-*Toxoplasma* antibodies IgG and IgM.[41] Anti-*Toxoplasma* antibody IgG was positive in 42% of patients versus 29% of the controls ($p<0.0001$). Anti-*Toxoplasma* antibody IgM was more prevalent in those patients positive for anti-phospholipid syndrome ($p<0.01$), systemic sclerosis ($p<0.05$) and inflammatory bowel disease ($p<0.05$) than the controls. In addition, anti-*Toxoplasma* antibody IgG was associated with antineutrophil cytoplasmic antibody-associated (ANCA) vasculitides ($p<0.01$), anti-phospholipid syndrome ($p<0.0001$), autoimmune thyroid diseases ($p<0.0001$), systemic sclerosis ($p<0.0001$), rheumatoid arthritis ($p<0.0001$). These findings support the concept that *Toxoplasma* may contributes to the pathogenesis of autoimmune disease.[2,41,42]

Chronic inflammatory bowel disease (IBD) is mainly of Crohn's disease and ulcerative colitis. IBD is an autoimmune with altered gut microbiome and an exaggerated immune response, with excess toxins released from gram negative lipopolysaccharid (LPS), bypassing the compromised and leaky inflamed gut mucosa.[43–45] Extensive use of biologicals and immunosuppressive agents in IBD patients elevates the risks to develop toxoplasmosis and other opportunistic diseases. The greatest danger for infections may link to the combination therapies with immunomodulators than individual drug therapy.[46] Crohn's patients are prone for gut abscess formation followed by toxoplsmosis and other infectious complications. IBD patients who are treated with corticosteroids, methotrexate, cyclosporine, azathioprine and anti TNF biological become more susceptible to infections. This informs physicians with IBD patients to be aware of the risks of infections including *Toxoplasma* and the strategies to minimize these complications in the patients.[2,46,47]

Exaggerated colonic inflammatory response is detected in pregnancy model for toxoplasmosis, with significant shortening in colonic length, infiltration of lymphocytes, and macrophages and microabscess formations in the cryptic structures in infected dams.[25,47,48]

Chemically induction IBD models for ulcerative colitis utilize oral administration of dextran sulfate sodium (DSS) for 3–16 cycles to provoke a chronic inflammatory response in the

gut[44] with elevated gram negative gut microbiota. Colitis causes significant increases in concentration of colonic LPS (550-fold). Likewise, *Toxoplasma* can cause ileitis with significant increased ileal concentrations of LPS (3,300-fold) $p < 0.01$.[49] Sera from IBD patients (120) and controls (100) were evaluated for antibodies for *Toxoplasma.* Anti-*Toxoplasma* titer was higher in IBD patients than controls suggesting *Toxoplasma* involvement in the pathogenesis of IBD, and specifically in Crohn's disease development.[50] *Toxoplasma* infection causes an extensive Th1 systemic inflammatory response to augment pro-atherogenic effects.[51,52] In fact, inflammation is required defensive mechanism against pathogens. But exaggerated and long lasting inflammatory response as in *Toxoplasma* infection can severely damage the tissues and organs as observed in patients with autoimmune diseases.[2,53]

Laboratory and Imaging Diagnostics

Rapid and accurate diagnostics are required for preventions and available therapeutic modalities. *Toxoplasma* infection can be confirmed using serological tests, polymerase chain reaction (PCR), and histological exams, and isolating the organisms as well as imaging analysis. Toxoplasmosis is mainly diagnosed by serological tests detecting anti-*Toxoplasma*-specific antibodies in the patients' sera samples. Most of the commercial serological kits currently available are based on *Toxoplasma* lysate antigens.[54] Laboratory tests measuring antibodies are less reliable in the immunosuppressed patients when diagnosis is based on clinical symptoms and during disease progression. In contrast, direct laboratory tests are useful to detect organisms and DNA by means of PCR in immunosuppressed patients.

Diagnosis of Maternal Congenital Toxoplasmosis

Maternal *Toxoplasma* infection is a serious risk factor for the fetus requiring 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 antibodies detections, but a limited screening program is used in Switzerland, Belgium, and Germany. Congenital and neonatal screening for toxoplasmosis are 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.[55] While, United States does not require routine screening, it is recommended that infants with serious systemic complications to be examined for toxoplsmosis.[56] 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 delivery.

Toxoplasmosis is diagnosed by serological exams based on the presence of IgM and IgG anti-*Toxoplasma* antibodies, and molecular techniques to detect organisms.[57] High levels of anti-*Toxoplasma* IgM antibody are detected during acute infection followed by a rise in IgG levels in 1–3 weeks. IgM or elevation of IgG anti-*Toxoplasma* antibodies suggest acute or reactivation and a possible transmission of *Toxoplasma* 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 is considered as “the international gold standard.” It is based on complement-lysis assay with relatively sensitive and specific for anti-*Toxoplasma* IgG antibody. This test is considered to be more reliable than available ELISA kits, but requires live organisms with each diluted serum analyzed under the microscope[58] which make it less safe diagnostic test in the laboratory environment.

α-Fetoprotein serum analysis is a biomarker released by embryonic hepatic cells to predict development and birth defects, and useful in prediction of feto-placental health and growth progression. Altered maternal α-fetoprotein level is associated with complication in pregnancy, hepatic, and tumor developments as well as fetal demise and resorption.[59] Indeed, α-fetoprotein serum analysis may be found useful in predicting immune responses and intrauterine death in toxoplasmosis.[60]

For infants with neurological disorders, and possible congenital infection anti-*Toxoplasma* IgM and IgA antibodies plus cerebrospinal fluid PCR are recommended to detect *Toxoplasma* DNA to provide a highly sensitive diagnostic tool for congenital toxoplasmosis.[61] CSF-PCR has been reported to be positive in 47% of ~60 infants from infected moms, while 0% positive in uninfected healthy ones. Additionally, western blot analysis is used to detect IgM and IgA[62] and RT-PCR for DNA in amniotic fluid with 98% sensitivity and 100% specificity.[57]

Imaging Examinations: CT and MRI scans can detect calcifications in the brain and multi-lesions are pathognomonic as major diagnostic modalities suggesting the presence of *Toxoplasma* encephalitis in neonates and pediatrics. Other major differential diagnostic may be required to differentiate from CNS lymphoma. Therefore, brain biopsy may be required in a patient with sporadic lesion with AIDS, or immunosuppressed patients.[63]

Currently Available and Experimental Anti-Toxoplasmosis Therapies

Toxoplasmosis is a neglected disease with no safe and effective therapy available for chronic persistent or pernicious fetal-maternal infection. Spiramycin has been used in feto-maternal toxoplasmosis prevention and treatment in Canada, Europe and Latin America for decades but is categorized as “experimental therapy” in United States. Spiramycin monotherapy is effective in early stages of pregnancy as a preventive measure but not after fetus is exposed to the infection. In a prospective cohort trial in Brazil 58% of newborns with moms treated with spiramycin, in contrast to over 73% from untreated ones ended up with congenital infection.[64] Over 50 percent of patients treated with spiramycin had retained *Toxoplasma* DNA in peripheral blood and remained infected.[65] In another clinical trial of the neonates from infected moms treated with spiramycin and pyrimethamine plus sulfadoxine, 24% of 257 children were diagnosed with congenital infection in France. Respectively, 7% were predicted to be infected in the first, 24% in the second, and 59% in the third trimesters.[66] Other feto-maternal therapies include azithromycin, clarithromycin, atovaquone, dapsone, and cotrimoxazole (trimethoprim-sulfamethoxazole), while their efficacies have not been established yet.[55]

Atovaquone and Maternal Congenital Toxoplasmosis

Atovaquone, a hydroxy-1,4-naphthoquinone and FDA approved, is fairly safe and effective treatment against tachyzoites and cyst forms of *Toxoplasma* and anti-*Plasmodial*.[67,68] It is used in adults, yet not approved for fetal-maternal and children toxoplasmosis.[69] Atovaquone is anti-fungal *Pneumocystic* pneumonia and anti-*Babesia microti*, causative of human blood-borne babesiosis endemic in New England and North Eastern States (e.g. New York, New Jersey, Rhode Island), North Midwest (e.g. Minnesota, Wisconsin) and California in the United States[70,71] Atovquone acts by targeting mitochondrial respiration and binds to the ubiquinol oxidation on cytochrome bc1 complex to block and to collapse the membrane in the organisms.[72,73] Atovaquone 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.[74] Atovaquone has been shown to protect against maternal congenital toxoplasmosis and inflammatory complications in murine model.[25] Atovaquone was superior to the standard of care with combined pyrimethamine plus sulfadiazine or pyrimethamine plus clindamycin therapies against brain inflammatory responses and the severity of infection in the mice.[68]

Diclazuril and Maternal Congenital Toxoplasmosis

Diclazuril [4-chlorophenyl [2,6-dichloro-4-(4,5-dihydro-3H-3,5-dioxo-1,2,4-triazin-2-yl)pheny l acetonitrile] is commonly used to prevent coccidiosis in poultry and livestock, from gastroenteritis, morbidity and mortality. *Toxoplasma and* coccidians are *Apicomplexan* with a highly conserved region of protochlorophyllide with traces of plant chloroplast epitope which is not present in humans or animals. Apicoplast is an extranuclear DNA organelle containing transcriptional and translational regions in *Toxoplasma* with specific enzymes unwinding DNA. It is presumably originated from eukaryotic *Ciliate* ancestors and prokaryotic green alga in evolution.[75] Apicoplast has a unique sensitivity to herbicidal agents with a safe and attractive region for drug discovery and vaccine target in *Toxoplasma* metabolic pathway, absent in the human and animals.

Diclazuril attaches to chloroplast epitope and the D1 protein of the *Toxoplasma* apicoplast without interacting to damage the mammalian host organs,[76] diclazuril downregulates expression of serine/threonine protein phosphatase in merozoites of *Eimeria* to induce apoptosis with possible mechanism of action against *Toxoplasma* organisms.[47,77,78]

Diclazuril a safe compound[77] when is administered orally and rapidly absorbed to attain steady state in blood as well as cerebrospinal fluid. Diclazuril is well tolerated and highly effective against feto-maternal toxoplasmosis.[47] Atovaquone protects against some aspects of gastrointestinal complications in experimental congenital toxoplasmosis in murine,[25] diclazuril was superior to atovaquone in improving anemia, colonic length and hepatic complications against maternal toxoplasmosis.[47] In addition, diclazuril and atovaquone combination therapy demonstrated a unique synergistic effect against severe toxoplasmosis and superior to monotherapy. Diclazuril in combination with atovaquone has shown a significant synergistic effect against severe infection in murine model. Clinical trials are required in maternal congenital as well as in ocular and chronic toxoplasmosis to prove

efficacy. Finally, diclazuril combination with atovaquone is anticipated to be used as a novel protective and preventive measure to eliminate the cycle of *Toxoplasma* infection in the definitive host, feline.

CONCLUSIONS

A century after discovery, *Toxoplasma* is still one of the most common and important causes of foodborne illnesses and congenital and pediatric disorders. *Toxoplasma* infects nucleated cells with a specific tropism for central nervous system and a mind bugging malicious effects. Congenital and neonatal toxoplasmosis pose the highest complications which include miscarriage, encephalitis, neurological retardation, mental illnesses, auditory and visual inflammatory disorders, cardiovascular abnormalities, and pains. Current available therapies are inefficient for congenital and chronic toxoplasmosis or have severe side effects with life threatening complications. There is an urgent need for effective and safe therapeutic modalities as well as possible effective vaccines to break the cycle and to eliminate the environmental infectious and resistant agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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