



Review Article

Congenital Toxoplasmosis: A Review of its Pathology, Immune Response and Current Treatment Options.

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ABSTRACT

Toxoplasmosis, caused by the protozoan parasite *Toxoplasma gondii*, is one of the most common parasites of man and other warm-blooded animals. Humans are infected through contaminated food, water, and blood transfusion, organ transplantation or from mother to foetus through the placenta. Severe congenital infections occur as a result of primary *T. gondii* infection in early pregnancy. Transmission of *T. gondii* to the foetus can result in serious health problems, including mental retardation, seizures, blindness and death. Frequency of foetal infection is higher when maternal infection occurs later in pregnancy and sequelae are more severe when maternal infections occur early in the first trimester of pregnancy. The ability of the parasite to survive intracellularly largely depends on the blocking of different proapoptotic signaling cascades of the host cells. During pregnancy, however, alterations in the incidence of apoptosis are associated with abnormal placental morphology and function. Both cellular and humoral immune responses control *T. gondii* infection. *Toxoplasma* is asymptomatic, infected women can only be detected by serological testing. In many instances, congenital toxoplasmosis can be prevented by educating pregnant women and women of childbearing age about the route of transmission. The need for screening suspected cases of *T. gondii* will help reduce transmission to the foetus.

Keywords: Toxoplasmosis, Congenital toxoplasmosis, Toxoplasmosis and immunosuppression. *Toxoplasma gondii*.

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INTRODUCTION

Toxoplasma gondii is an intracellular coccidian parasite that belongs to the phylum Apicomplexa. The parasite is globally distributed and can be found within many different species of mammals and birds. It is an obligate intracellular parasite with properties similar to the pathogen that causes malaria. *T. gondii* infects a large proportion of the world's population but uncommonly causes clinically significant disease. Toxoplasmosis is usually an asymptomatic disease, but often takes

a severe and life threatening course during pregnancy, in foetuses, new born babies, and in immunocompromised patients (Robert-Gangneux *et al.*, 2009). Most cases of toxoplasmosis in the immunocompetent hosts are subclinical or benign. The most severe symptoms occur in the congenitally acquired form and in immune deficient individuals. Toxoplasmosis in immunocompetent host can be classified as congenital, acquired or ocular.

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Foetal infection with *T. gondii* may result in stillbirth or abortion. Congenital infection is most severe if acquired in the first or, in some cases, second trimester of pregnancy. Infection during the second or third trimester tends to be asymptomatic. It may lead severe CNS impairment, which might not manifest for several years. Infection in children without evidence of exposure to *T. gondii* has been recorded (Varella *et al.*, 2009). Domestic cats are the definite host of *T.gondii*. Infected faeces of cats containing the oocysts contaminate the food of man thus commencing the life cycle. *Toxoplasma gondii* life cycle has three forms: tachyzoite, bradyzoite, and sporozoite. During the acute stage of *T.gondii* infection, tachyzoites invade and replicate within cells and are responsible for congenital infection. The tachyzoites invade all organs, especially the muscle (including the heart) liver, spleen, lymph nodes and central nervous system (CNS). During the latent infection, bradyzoites are present in tissue cyst. Sporozoites are found in environmentally resistant oocysts formed after the sexual stage of life cycle.

Patients with acquired toxoplasmosis can present with a range of clinical manifestation, from subclinical lymphadenopathy, which is the most common presentation, to fatal, fulminant disease. In the immunocompetent host, infection with *T. gondii* may be indistinguishable from infectious mononucleosis (Hoeprich *et al.*, 1994). Clinically reactivated toxoplasmosis is usually due to the reactivation of latent *T. gondii* infection; therefore all AIDS patients with *T. gondii* antibodies are at risk of developing active infection (Hoeprich *et al.*, 1994). In most African countries, sufficient attention is yet to be given to toxoplasmosis. Therefore, this review highlights the pathology of congenital toxoplasmosis and other forms of toxoplasmosis, immune-response and current treatment options.

PREVALENCE OF TOXOPLASMOSIS AND MODE OF TRANSMSSION

Toxoplasma gondii infection is widespread in humans although its prevalence varies widely from place to place and it is estimated that up to fifty million people worldwide are infected. Overall, less than 0.1% of the general population has been studied to be infected congenitally (Choi *et al.*, 1997; Evengard *et al.*, 1999). Reported birth

prevalence with congenital toxoplasmosis ranges from one to ten per 10,000 live births (Evengard *et al.*, 2001). There has been an increase in seroprevalence to *Toxoplasma* antibodies among pregnant women in Cali, Colombia, for the past 25 years (Rosso *et al.*, 2008). *Toxoplasma* antibody serological tests using the Dye test on sera of pregnant and postpartum Nigerian women showed prevalence rates that ranged from 72.5% to 88.8% (with an overall rate of 75.4%), and 75.0% to 94.4% (with an overall rate of 80.5%) respectively (Onadeko *et al.*, 1996).

Toxoplasma gondii is transmitted by three principal routes. First, human can acquire *T.gondii* by eating raw or inadequately cooked infected meat, especially pork, mutton, and wild game, or uncooked foods that have come in contact with infected meat (Dubey, 1994). Second, humans can inadvertently ingest oocysts that cats have passed in their faeces, either from a litter box or from soil (e.g. soil from gardening, unwashed fruits or vegetables in unfiltered water). Third, women can transmit the infection transplacentally to their unborn foetus. Transplacental infection occurs when an uninfected mother acquires infection during pregnancy. First, there is a parasitaemia in the mother, the invasion of placenta, and finally *T gondii* spreads to foetal tissues. Transmission of *T.gondii* may also occur through blood transfusions and organ transplants. Oocysts contamination of the environment is widespread as oocysts are shed by domestic cats and other members of the Felidae (Dubey and Beattie, 1988). Domestic cats are probably the major source of contamination since oocysts formation is greater in domestic cats. Cats may excrete millions of oocysts after ingesting only one bradyzoite or one tissue cysts, and many tissue cysts may be present in one infected mouse (Dubey, 2001).

Toxoplasma gondii is common in many animals used for food, including sheep, pigs and rabbits. It may survive in food animals, in tissue cysts for years (Hill and Dubey, 2000). Virtually all-edible parts of an animal can harbour viable *T.gondii*. Viable *T.gondii* infection was isolated from 17% of 1000 adult pigs from a slaughter plant in Iowa (Dubey and Odening, 1995). *Toxoplasma* antibodies were detected in sheep, goat and pigs

in serological survey carried out in Kano, Nigeria (Okoh *et al.*, 1981). The largest outbreak of municipal water reservoir in British, Columbia, and Canada (Isaac-Renton *et al.*, 1998). The water reservoir was thought to be contaminated with *T.gondii* oocysts excreted by cougars (*Felis concolor*) (Aramini *et al.*, 1999). The cultural habits of a population have been known to affect the acquisition of *T.gondii* infection from ingested tissue cysts in undercooked meat. French habit of eating some meat products raw or undercooked led to high incidence of *T.gondii* infection in humans in France (Dubey, 1988).

***Toxoplasma gondii* Genotypes and Pathology**

Worldwide genotypic analysis of *T.gondii* isolates identified population structure consisting of three widespread clonal lineages termed type I, II and III (Howe and Sibley, 1995; Ferreira Ade *et al.*, 2006). It was proposed that the different genotypes may be partly responsible for the different pathogenicities observed in the infection as Type II strains are known to have overall prevalence in human infections, whereas type I strains are over represented in studies of congenital toxoplasmosis (Howe and Sibley, 1995). Type I strains in mice, were noticed to rapidly disseminate and reach high tissue burden even from very low initial inoculums, and it was reported to be the most virulent (Mordue *et al.*, 2001). The abundance of type I and recombinant strains in patients with retinochoroiditis have been seen in Brazil (Ferreira Ade *et al.*, 2006). In addition, type I and III strains were observed to be the cause of ocular disease (Ferreira Ade *et al.*, 2006). The enhanced ability in type I strains to cross biological barriers likely represents an important advantages in the establishment of disseminated infection. However, both pathogenic and apathogenic isolates have been observed in a study in Brazil belonging to genotype I (Peyron *et al.*, 2006).

The ability of the parasite to survive intracellularly largely depends on the blocking of different proapoptotic signaling cascades of the host cells. During pregnancy, however, alterations in the incidence of apoptosis are associated with abnormal placental morphology and function. In a study to evaluate the incidence of apoptosis and cell proliferation in trophoblastic (BeWo cell line) and uterine cervical (HeLa cell line) cells infected

clinical toxoplasmosis in humans was epidemiologically linked to drinking water from a with a highly virulent RH strain or a moderately virulent ME49 strain of *T. gondii*. Angeloni *et al.* (2009) reported that RH and ME49 strains of *T. gondii* possess opposing mechanism of interference in apoptosis and cell cycle S phase of both BeWo and HeLa cells and these differences can be associated to evasion strategies of the parasite to survive inside the host cells. In humans, clinical disease is normally limited either to immunocompromised individuals or to congenital disease resulting from an acute infection of the expectant mother. The severity of congenital infections depends on the stage of pregnancy when the acute infection occurred, and spontaneous abortions or neurological disorders such as blindness and mental retardation could occur (Black and Boothroyd, 2000).

Toxoplasma gondii has the ability to invade and to establish productive infection in almost all nucleated cell. The initial step of the parasite invasion process is recognition and attachment to the target cell. Upon encountering the host cell, the parasite will survey the membrane until an appropriate point of attachment is recognized by the apical pole. Host cell lamini, parasite surface lectins and major parasite surface protein may participate in preliminary attachment of parasite to host cell (Kasper and Mineo, 1994). Two types of organelle (rhoptries and micronemes) at the anterior end of the parasite appear to be involved. Rhoptries are found to be discharged at the time of invasion while micronemes may discharge their contents immediately preceding or during invasion (Manger *et al.*, 1998). Two microneme proteins that contain thrombospondin-like domains may function in adherence following their release on the surface of the parasite (Wan *et al.*, 1997).

The effect of *Toxoplasma* infection on any given person may differ, depending on factors such as: individual genetic predisposition, the state of the immune system, the parasite doses, the virulence of the infecting strain, the timing of infection (e.g. infection in the first trimester, prenatal and postnatal infections) and the part of the brain affected (Singh *et al.*, 1998; Torrey and Robert, 2003). It has been reported that congenitally

acquired toxoplasmosis is more severe than postnatal acquired infection (Singh, 2003). Some sequelae of congenital toxoplasmosis are not apparent at birth and may not become apparent until the second or third decade of life (Torrey and Robert, 2003). Therefore, the severity and likelihood of infection is dependent on the trimester of pregnancy and if the mother has become infected with *T.gondii*. The severity of toxoplasmosis infection in an infant whose mother becomes infected during the first trimester is higher than during the third trimester (Singh, 2003). Symptomatic infants present with a combination of fever, microcephaly or hydrocephalus, hepatosplenomegaly, jaundice, chorioretinitis and seizures. Pneumonitis, myocarditis, thrombocytopenia, mono and lymphocytosis, and a maculopapular rash are also known to occur (Martin, 2000). Children may be asymptomatic with sequelae such as chorioretinitis, mental retardation, seizures and nerve palsies during the neonatal period (Peyron *et al.*, 1996). Chorioretinitis has been reported to occur later in life in some infants and this has also been discovered in adolescence (Peyron *et al.*, 1996).

Toxoplasma initially crosses the intestinal epithelium, disseminates into the deep tissue, and transverse biological barriers such as the placenta and the blood brain barrier to reach immunologically privileged sites where it causes the most severe pathology. Varieties of cell types including intra epithelial leucocytes in the intestine are known to be invaded during histopathological studies of *Toxoplasma* (Dubey *et al.*, 1997). Crossing biological barriers, including the intestine, the blood barrier and the placenta, leading to dissemination within the host is a prerequisite for the establishment of *T.gondii* infections. Ingested parasites (oocysts or bradyzoite in tissue cysts) invade the intestine and differentiate into tachyzoites followed by spread of the organism haematogenously and via lymphatic tissue (Dubey, 1997). Tachyzoites are known to play important role in the pathogenesis of acute toxoplasmosis (Robert and Mcleod, 1999) and in reactivation of chronic infection in human (Reiter *et al.*, 2000).

Toxoplasma crosses epithelial barriers to gain access to deeper tissues including the brain, the

placenta and the retina. *Toxoplasma* tachyzoites use active motility to cross polarized cell layers and extracellular matrix (Howe and Sibley, 1995). This suggests that active parasite migration is an important component of dissemination during toxoplasmosis. Active motility is not only used for cell invasion but also provide the parasite with an effective mechanism of dissemination in its micro environment within tissues (Howe and Sibley, 1995). Although most congenitally infected children are asymptomatic at birth, they may develop some symptoms later in life. Hydrocephalus, chorioretinitis, intracerebral calcification, pancytopenia, and death may occur (Remington *et al.*, 1995; Singh *et al.*, 1998). Loss of vision was reported to be the most common sequela in congenitally infected children (Remington *et al.*, 1995).

There are indications that most ocular disease from *T.gondii* is caused by infection after birth. Silveria *et al.* (2001) showed that ocular toxoplasmosis is due to acute infection after birth because the rate of infection in young children was low. Although, postnatally acquired infections were reported to be asymptomatic, manifestations of toxoplasmosis include large lymph nodes (particularly of the cervical region) headaches, muscles aches and sore throat (Hunter and Remington, 1994). Subclinical forms of toxoplasmosis have also been observed in children at birth, without higher incidence of prematurity or low weight at birth. The main neurological sequela observed among the children was a delay in their neuro-psychomotor development (Safadi *et al.*, 2003).

When infection occur for the first time during pregnancy, mother to child transmission of the parasite could cause congenital toxoplasmosis. The risk of transmission depends on the gestation at maternal infection, rising from approximately 6% for women infected at 10 weeks of gestation to 80% if the infection occurred at 38 weeks (Dunn *et al.*, 1999). Transplacental passage is more common when maternal infection occurs in the latter half of pregnancy, but foetal injury is usually less severe. It may lead to miscarriage, stillbirth, or congenital defects depending on the stage of gestation when the infection occurs (Gagne, 2001). Robert *et al.*, (1999) reported that the frequency of foetal infection is higher when

maternal infection occurs later in the pregnancy (e.g. third trimester). Most children with congenital toxoplasmosis appear developmentally normal but up to 3% have evidence of permanent neurological damage or bilateral visual impairment (Dunn *et al.*, 1999). Placental contamination is a pre-requisite to congenital infection when there is maternal parasitaemia. The infected placenta then acts as a reservoir from which the parasite can spread to the foetus leading to multi-systemic disease (Daffos *et al.*, 1988).

Toxoplasmosis is known to be a lifelong condition. When the mother is chronically infected with *T.gondii*, the parasite is dormant in maternal tissues and there is no parasitaemic phase. Foetal transmission can occur immediately after maternal infection or be delayed by weeks (Martins, 2000). *Toxoplasma* infection in early pregnancy leads to miscarriage or intra-uterine death. In foetuses that survive, lesions are predominantly cerebral due to cerebral vasculitis and necrosis. The earlier the infection occurs in pregnancy, the worse the outcome is for the foetus, both in term of survival and sequelae, (Martins, 2000). Women who are seropositive before conception have the least risk of congenital toxoplasmosis while the greatest risk of congenital toxoplasmosis occurs during the first trimester of pregnancy (Remington *et al.*, 1995; Evengard *et al.*, 1999). However, the highest level of transmission of congenital toxoplasmosis occurs in the third trimester. This is thought to be related to the much larger size of the uterus. If a woman's foetal loss is as a result of *T.gondii* infection; her subsequent pregnancies are safe as far as the parasitic infection is concerned until she becomes immunocompromised during subsequent pregnancies.

Although, transmission of congenital toxoplasmosis by an immunocompetent woman infected before conception, to her foetus had been reported (Villena *et al.*, 1998). Practically, only mothers with primary infection acquired during pregnancy are known to be at risk. If the infection was acquired before conception, there is no practical risk of congenital transmission (Martins, 2000).

However, a *T. gondii* strain involved in re-infection was isolated, characterized, and studied in an

experimental mouse model that suggested immunity against type II strain may not be protective against a re-infection with a different genotype, especially if it is atypical (Elbez-Rubinstein *et al.*, 2009).

Congenital Toxoplasmosis: Severity of Foetal Disease

The severity of foetal disease varies inversely with the gestational age at which maternal infection occurs.

Without *Toxoplasma*-specific chemotherapy, most foetuses infected early in pregnancy die *in uteri* or in the neonatal period, or have severe neurologic and ophthalmologic disease (Lynfield and Guerina, 1997). Nearly all foetuses infected in the second and third trimesters have mild or subclinical disease in the newborn (Lynfield and Guerina, 1997). The principal clinical findings for infants and children who had symptomatic infection invariably had some degree of central nervous system (CNS) involvement and often had significant retinal disease. Approximately two thirds of them had disease primarily limited to the CNS and eyes; one third had more generalized findings. Infants who had primary neurologic disease typically had intracranial calcifications, abnormal cerebrospinal fluid (CSF) profiles, chorioretinitis, and convulsions. Infants who had signs and symptoms of generalized disease had hepatosplenomegaly, lymphadenopathy, hyperbilirubinaemia, and anaemia in addition to CSF abnormalities and chorioretinitis (Lynfield and Guerina, 1997).

Ocular Toxoplasmosis

Toxoplasma gondii is the most common cause of infectious chorioretinitis in immunocompetent children and adults. It is also an important cause of ocular disease in immunocompromised patients (Peyron *et al.*, 1996). Most cases are believed to result from local reactivation of congenital infection, but high rates of chorioretinitis have been described to be due to postnatally acquired toxoplasmosis (Lynfield and Guerina, 1997). Acute *Toxoplasma* chorioretinitis is usually subclinical in healthy children and adults, but severe complications, including visual impairment or glaucoma, may occur in some cases (Lynfield and Guerina, 1997). Several mechanisms for onset of retinal disease in congenital infection have been proposed, including invasion of the eye following recurrent parasitaemia, the onset of an

inflammatory reaction to old retinal tissue cysts, and a hypersensitivity reaction to *Toxoplasma* antigens localized in the retina. The peak incidence of relapsing chorioretinitis following congenital infection is in the second and third decades of life (Lynfield and Guerina, 1997).

Toxoplasmosis in the Immunocompromised Host

Two types of infection are seen: recrudescence of chronic infections, occurring in patients with *Toxoplasma* antibody and AIDS (acquired immunodeficiency syndrome) and severe primary infection.

Rupture of cysts in immunocompromised hosts result in disease reactivation, including encephalitis or disseminated toxoplasmosis (Jones *et al.*, 2003). Chronic toxoplasmic encephalitis may occur when a person's immune system is impaired. Indeed, toxoplasmic encephalitis marked by dementia and seizures has become the most commonly recognized cause of central nervous system opportunistic infections in AIDS patients. Additionally, it appears that certain cancer treatments weaken the immune system and old infections in the muscles could become reactivated, causing severe complications or death (Shirtmatter *et al.*, 1992). Most cases are relapses of chronic infections, caused by AIDS or immunosuppressive drugs that impair cellular immunity, especially corticosteroids and cyclophosphamide.

Primary infections occur in immunosuppressed patients by natural routes, by heart transplant, or leukocyte transfusion. They involve many organs, and tend to be more severe. The usual predisposition factors are in patient receiving immunosuppressive drugs, and rarely, early undiagnosed leukemia, lymphoma, or AIDS infection. Patients with such impaired immunity are likely to experience reactivation of latent disease than to acquire new infections (Pedrol *et al.*, 1990). The increasing use of highly immunosuppressive chemotherapy and conditioning regimens (including rituximab, fludarabine and anti-thymocyte globulin) was reported to be associated with a significant risk of toxoplasmosis in patients after allogeneic

haematopoietic stem cell transplantation (HSCT) (Rusiňáková *et al.*, 2009).

IMMUNE RESPONSE TO CONGENITAL TOXOPLASMOSIS

The immune system has a crucial role in both the course of the infection and in the evolution of toxoplasmosis disease. In particular, IFN-gamma plays an important role in resistance to toxoplasmosis. Polymorphisms in genes encoding cytokines have been shown to have an association with susceptibility to parasitic diseases (de Albuquerque *et al.*, 2009). Natural immunity against *T.gondii* is dependent on the induction of strong parasite specific immunity in the host (Sher *et al.*, 1995). The rapid migration of neutrophils to site of infection is thought to be important for parasite control before adaptive immunity is established (Del Rio *et al.*, 2001). *Toxoplasma* actively infects leukocytes *in vitro* and tachyzoites have also been identified within leukocytes in the murine intestine (Dubey *et al.*, 1997; Channon *et al.*, 2000) and therefore the presence of leukocytes may have contributed to the dissemination of intracellular parasites (Shaw *et al.*, 1998).

CD8+ and/or CD4+ T cells play synergistic role in the acquisition of protective immunity against *Toxoplasma* infection. Immune CD8+ T cells from both infected mice or human secrete interferon gamma (IFN- γ) and exhibit *in vitro* cytotoxicity towards infected cells (Khan *et al.*, 1990). T-helper (Th-1) CD4+ T cells produce IFN- γ and IL-12, while T-helper (Th-2) cells produce IL-4, IL-5 and IL-10 which are associated with down regulation of parasitic cell mediated immune response (Mosmann and Moore, 1991). The roles of natural killer cells (NK) and IFN- γ were shown to reduce maternal infection, perhaps because of inhibition of tachyzoite replication. Also increased in number of killer cells in mice partially protects against congenital *Toxoplasma* transmission (Remington *et al.*, 1995).

Both cellular and humoral immune response control parasite virulence and tissue tropism which may be strain specific. Macrophages are involved in the regulation of cellular immunity through their production of immunologic mediators. Tachyzoites stimulate macrophages to produce interleukin-12 (IL-12). IL-12 in turn

activates NK cells and T-cells to produce interferon gamma and it is this early produced interferon-gamma that is crucial for resistance. The combination of IFN- γ and tumour necrosis factor (TNF) mediate killing of tachyzoites by macrophages (Kahn *et al.*, 1996). The production of nitric oxide may however, have opposing effects. Nitric oxide production protects against *T. gondii* infection and at the same time limits the immune response probably contributing to the establishment of the chronic state (Hayashi *et al.*, 1996).

In a recent study by Matowicka-Karna *et al.* (2009) that evaluated Th2 humoral response (IL-5, IL-6, IL-10) and Th1 cell response (IL-12, TNF-alpha) in patients infected with *T. gondii*, they reported twofold higher levels of IL-5 and IL-6 as compared to healthy subjects, which seemed to confirm the presence of an inflammatory state. They also found that the level of IL-10 was fivefold higher in the course of toxoplasmosis than in healthy controls. The levels of IL-12 and TNF-alpha were comparable to those observed in healthy controls. The study thus revealed that patients infected with *T. gondii* showed increased production of the humoral response cytokines, whereas the generation of the cell response cytokines remained unchanged (Matowicka-Karna *et al.*, 2009).

The analyses of the occurrence of polymorphisms in the gene encoding IFN-gamma (+874T/A) among *Toxoplasma gondii* seropositive individuals, including those with ocular lesions caused by the parasite was conducted by de Albuquerque *et al.* (2009) so as to verify the polymorphisms that could be related to susceptibility to the development of ocular toxoplasmosis. They reported that the differences between A and T allele distributions were not statistically significant between the two groups. However, it was observed that a higher frequency of individuals from the ocular group possessed the A/A genotype, when compared with the control group, suggesting that homozygosity for the A allele could enhance susceptibility to ocular toxoplasmosis in *T. gondii* infection (de Albuquerque *et al.*, 2009).

DIAGNOSIS AND TREATMENT

When toxoplasmosis infection is suspected in a woman during pregnancy or before pregnancy, the diagnosis is primarily made by serological investigation (Pinon *et al.*, 2001). Detection of *Toxoplasma* specific antibodies is the primary diagnostic method in determining the parasite infection. Different serological tests have been used to detect antibodies to the parasite. *T. gondii* specific IgG, IgM, IgA or IgE antibodies can be detected with the serological methods. Newborn infants suspected of congenital toxoplasmosis should be tested by both an IgM and IgA capture enzyme immunoassay. In cases of congenital infection, however, antibody responses may be delayed in some infants, and the presence of transplacentally transferred maternal IgG may interfere further with the serologic confirmation of infection. For these reasons, all infants known to be at risk for congenital infection should be evaluated further for clinical signs of infection (chorioretinal lesions, intracranial calcifications, or hydrocephalus) (Lynfield and Guerina, 1997). Classically, serodiagnosis includes titration of specific immunoglobulin G (IgG) showing past exposure and screening for specific IgM, which is suggestive of recent exposure or ongoing active infection. IgM detection could be due to naturally interfering IgM or persistence of IgM for long time after primary infection (Suzuki *et al.*, 2001). *Toxoplasma* infection can also be detected with the use of polymerase chain reaction (PCR) test for DNA determinants. PCR is most often used in testing the amniotic fluid to determine whether the foetus of an infected pregnant woman is infected (Jones *et al.*, 2003).

Screening during pregnancy is of importance in preventing congenital infections and in diagnosing all infected infants. Since most congenitally infected infants appear normal at birth, screening for toxoplasmosis is helpful in identifying women who are non-immuned at the beginning of their pregnancy. Screenings for presence of antibodies allow primary prevention of toxoplasmosis infection where eating habit and hygiene practices have been identified as risk factors (Martins, 2000). All suspected patients should be initially tested for presence of *Toxoplasma* specific IgG antibodies to determine their immune status. Presence of IgG antibodies only signify exposure because asymptomatic humans can develop very high *T. gondii* antibody titers and titer may remain high for many years or even whole year if

repeated exposures are encountered. Recent infection can be identified by an 8-fold rise in antibodies titer; taken two weeks apart (Pinon *et al.*, 2001).

Sulphadiazine and pyrimethamine are the two drugs that are widely used for the treatment of toxoplasmosis. These drugs have beneficial effect on toxoplasmosis when given in the acute stage but when there is active multiplication of the parasites, they will usually not eradicate infection (Guerina *et al.*, 1994). The employment of combined drugs is known to be principally effective on the actively multiplying tachyzoites. When infection *in utero* is documented using PCR on an amniotic fluid sample, the mother should be started on a combination of pyrimethamine and sulphadiazine with folic acid supplementation. Good outcome has been reported with the use of high-dose pyrimethamine, clindamycin, co-trimoxazole and folic acid in patients after allogeneic haematopoietic stem cell transplantation (HSCT) (Rusiňáková *et al.*, 2009).

Infected infants should be treated after birth up to one year of age with the same drugs whether the infection is over or latent and follow up is important up to adolescence (Martin, 2000).

Severe ocular forms of toxoplasmosis are also usually treated with the standard regimen but sulfadiazine may be substituted by clindamycin. The preferred treatment in immunocompromised patients is the standard combination of pyrimethamine and sulfadiazine. However, due to frequent serious side effects, alternative treatments are possible. In some patients, especially those undergoing immunosuppression due to stem cell transplantation, primary prophylaxis of cerebral toxoplasmosis is achieved by co-trimoxazole. Reduced doses of the standard regimen may be used as secondary prophylaxis during severe immunosuppression in these patients. However, due to an increased risk of myelotoxicity, other therapeutic measures have to be used (Prášil, 2009).

PREVENTION OF TOXOPLASMA INFECTION IN WOMEN

Proper washing of hands after handling meat, poultry or seafood with soap and water before doing other task will prevent *Toxoplasma* infection in human beings. (Dubey and Beattie, 1988). It is

also important for pregnant women to wear gloves when they are gardening or touching soil or sand, because of possible presence of cat faeces. Afterwards they should wash their hands thoroughly (Jones *et al.*, 2003). Healthcare workers should educate women of childbearing age on information about *T.gondii* transmission. At the first prenatal visit, health care provider should educate pregnant women about food hygiene and if possible, pregnant women should avoid exposure to cat faeces (Jones *et al.*, 2003). In the last few years, there has been considerable progress towards the development of a vaccine for toxoplasmosis, and a vaccine based on the live-attenuated S48 strain was developed for veterinary uses (Kur *et al.*, 2009). However, this vaccine is expensive, causes side effects and has a short shelf life. Furthermore, this vaccine may revert to a pathogenic strain and, therefore, is not suitable for human use. Various experimental studies have shown that it may be possible to develop a vaccine against human toxoplasmosis (Kur *et al.*, 2009).

IMPLICATIONS FOR CURRENT PRACTICE AND FURTHER RESEARCH

Presently, there is no evidence of prenatal screening or neonatal screening in Nigeria and in most African countries. This issue needs to be revisited to prevent morbidity and mortality due to toxoplasmosis especially considering the pathology due to toxoplasmosis. This is imperative in settings where domestic cats are common. Further research is needed to determine the risk of neurological or visual impairment in infected children and whether the risk or severity of impairment can be reduced by prenatal or postnatal treatment.

Serological screening for specific antibodies to *Toxoplasma* will reduce the transmission of toxoplasmosis to foetus. Women with HIV infection should be screened for toxoplasmosis because of the risk of *T. gondii* reactivation and toxoplasmic encephalitis (Jones *et al.*, 2003). Reliable information is needed on the prevalence of the disease in most African countries. Mortality and morbidity due to postnatally acquired toxoplasmosis, both in immune competent and deficient people far exceeds the burden of the disease due to congenital toxoplasmosis (Gilbert and Stanford, 2000).

Primary prevention of toxoplasmosis in the general population may have a much greater impact on the morbidity and mortality due to toxoplasmosis than strategies confined to pregnant women. Primary prevention is needed to tackle major sources of infection such as infected meat and meat products (Cook *et al.*, 2000).

CONCLUSION

The clinical manifestation of congenital transmission includes: chorioretinitis, hydrocephalus and intracranial infection. *T gondii* acquired during pregnancy may be transmitted to the foetus and may cause inflammatory lesions that may lead to permanent neurological damage, with or without hydrocephalus, and chorioretinitis with visual impairment. Congenital toxoplasmosis is an important cause of morbidity and mortality among immunocompromised patients and can cause foetal infection with unpredictable manifestations in the foetus and neonate if it is acquired during pregnancy. Toxoplasmosis can lead to severe sequelae for the foetus and the newborn with death. Sequelae are more severe when maternal infection occurs early in first trimester. Frequency of foetal infection is higher when maternal infection occurs later in pregnancy.

Pregnant women and the infected newborns are often asymptomatic though they stand the risk of having recurring chorioretinitis later in life. *Toxoplasma gondii* infections in pregnancy should be a notifiable disease for clinicians and researchers in African countries. Follow-up of infected children should be performed as part of a quality control programme of screening. Women should be enlightened on how to avoid *Toxoplasma* infection. Prospective and randomised trials are also needed to properly manage congenital toxoplasmosis.

REFERENCES

Angeloni MB, Silva NM, Castro AS, Gomes AO, Silva DA, Mineo JR and Ferro EA (2009). Apoptosis and S phase of the Cell Cycle in BeWo Trophoblastic and HeLa Cells is Differentially Modulated by *Toxoplasma gondii* Strain Types. *Placenta*. July 28. [Epub ahead of print] doi:10.1016/j.placenta.2009.07.002. In Press

Aramini JJ, Stephen C and Dubey JP (1999). Potential contamination of drinking water with

Toxoplasma gondii oocyst. *Epidemiol. Infect.* **122**:305-315.

Black MW and Boothroyd JC (2000). Lytic Cycle of *Toxoplasma gondii*. *Microbiol. Mol. Biol. Rev.* **64**: 607–623

Channon JY, Seguin RM and Kasper LH (2000). Differential infectivity and division of *Toxoplasma gondii* in human peripheral blood leukocytes. *Infect. Immunol.* **68**: 4822-4826.

Choi WY, Nam HW, Kwak NH, Huh W, Kim JR, Kang MW, Cho SY and Dubey JP (1997). Foodborne outbreaks of human toxoplasmosis. *J. Infect. Dis.* **175**: 1280-1282.

Cook AJ, Gilbert RE, Buffano W, Zuffrey J, Petersen E, Jennum PA, Foulon W, Semprini AE, Dunn DT (2000). Sources of toxoplasma infection in pregnant women: European multicenter case-control study. European Research Network on congenital Toxoplasmosis. *BMJ.* **321**: 142-147

Daffos F, Foresstier F, Capella – Pavlovsky M, Thulliez A, Aufrant C, and Valenti D (1988). Prenatal management of 746 pregnancies at risk for congenital toxoplasmosis. *N. Engl. J. Med.* **318**: 271-275.

de Albuquerque MC, Aleixo AL, Benchimol EI, Leandro AC, das Neves LB, Vicente RT, Bonecini-Almeida Mda G, Amendoeira MR (2009). The IFN-gamma +874T/A gene polymorphism is associated with retinochoroiditis toxoplasmosis susceptibility. *Mem Inst Oswaldo Cruz.* **104**: 451-455

Del Rio I, Bennouna S, Salinas J and Denkers EY (2001). CXCR2 deficiency confers impaired neutrophils recruitment and increased susceptibility during *Toxoplasma gondii* infection. *J. Immunol.* **167**: 6503-6509.

Dubey JP (1988). Refinement of pepsin digestion method for isolation of *Toxoplasma gondii* from infected tissues. *Vet. Parasitol.* **74**:75-77.

Dubey JP and Beattie CP (1988). *Toxoplasmosis of Animals and Man* Boca Raton, FL: CRC Press.

Dubey JP (1994). *Toxoplasmosis*. *J. Am. Vet. Med. Assoc.* **205**: 1593-1598.

Dubey JP and Odening K (1995). Toxoplasmosis and related infections: In: Samuel WM, Pybus MJ, Kocan AA eds. *Parasitic Diseases of Wild mammals*. Ames IA: Iowa State University Press: 478-519.

Dubey JP (1997). Bradyzoite – Induced murine toxoplasmosis: Stage conversion pathogenesis, and tissue cyst formation in mice fed bradyzoites of different strains of *Toxoplasma gondii*. *J. Eukaryot. Microbiol.* **44**: 592-602.

Dubey JP, Speer CA, Shen SK, Knok OCH and Blixt JA (1997). Oocyst induced murine toxoplasmosis: life cycle, pathogenicity and stage conversion in mice fed. *Toxoplasmosis gondii* oocysts. *J. Parasitol.* **83**: 870-882

Dubey JP (2001). Oocyst shedding by cats fed isolated bradyzoites and comparison of infectivity of bradyzoites of the VEG strain. *Toxoplasma gondii* to cat and mice. *J. Parasitol.* **87**: 215-219. Dunn D, Wallon M, Peyron F, Peterson E, Peckham C, and Gilbert R (1999). Mother to child transmission of toxoplasmosis: risk estimates for clinical counseling. *Lancet.* **353**: 1829-1833

Elbez-Rubinstein A, Ajzenberg E, Dardé M, Cohen R, Dumètre A, Year H, Gondon E, Janaud J, Thulliez P (2009). Congenital toxoplasmosis and re-infection during pregnancy: case report, strain characterization, experimental model of re-infection, and Review. *J. Infect. Dis.* **199**: 280-285

Evengard B, Lilja G, Capraru T, Malm G, Kussofsky E, Oman H, and Forsgren MA (1999). Retrospective study of seroconversion against *T. gondii* during 3,000 pregnancies in Stockholm. *Scand. J. Infect. Dis.* **31**: 127-137.

Ferreira Ade M, Vitor RW, Gazzinelli RT and Melo MN (2006). Genetic analysis of natural recombinant Brazilian *Toxoplasma gondii* strains by multilocus PCR-RFLP. *Infect. Genet. Evol.* **6**:22-31

Gagne SS (2001). Toxoplasmosis. *Prim Care Update Obstet. Gynecol.* **8**: 122-126.

Guerina NG, Hsu HW, Meissner HC, Maguire JH, Lynfield R and Stenchenberg B (1994). Neonatal serologic screening and early treatment for

congenital *Toxoplasma gondii* infection. The new England Regional Toxoplasma Working Group. *New Engl. J. Med.* **330**: 1858-1863

Hayashi S, Chan CC, Gazinelli R and Roberge FG (1996). Contribution of nitric oxide to the host parasite equilibrium in toxoplasmosis. *J. Immunol.* **156**: 1476-1481.

Hill D and Dubey J P (2000). *Toxoplasma gondii*: transmission, diagnosis and prevention. *Clin. Microbiol. Infect.* **8**: 634-640.

Hoeprich PD, Jordan MC and Ronald AR (1994). Infectious Diseases: *A treatise of infectious processes*. Lippin colf-Raven publishers. Pp: 1201-1213.

Howe DK and Sibley LD (1995). *Toxoplasma gondii* comprises three clonal lineages: correlation of parasite genotype with human disease. *J. Infect. Dis.* **172**: 1561-1566.

Hunter CA and Remington JS (1994). Immunopathogenesis of Toxoplasmic encephalitis. *J. Infect. Dis.* **179**:1057-1067.

Isaac – Renton J, Bowie WR and King A (1998). Detection of *Toxoplasma gondii* oocysts in drinking water. *Appl. Environ.* **64**: 2278-2280.

Jones J, Lopez A and Wilson M (2003). Congenital Toxoplasmosis. *J. Am. Family Phy.* **67**: 2131-2138.

Jones BL, Torrey EF, and Yolken R (2003). Drugs in the treatment of schizophrenia and bipolar disorder inhibit the replication of *Toxoplasma gondii*. *Schizophr. Res.* **62**: 237-244.

Kahn IA, Maturra T and Kasper LH (1996). IL-12 enhances murine survival against acute toxoplasmosis. *Infect. Immun.* **61**:1976-1980.

Kahn IA, Smith KA, and Kasper LH (1990). Induction of antigen specific human cytotoxic T cells by *Toxoplasma gondii*. *J. Clin. Invest.* **85**:1879-1885

Kasper LH and Mineo JR (1994). Attachment and invention of host cell by *Toxoplasma gondii* *Parasitol. Today.* **10**: 82-85.

- Kur J, Holec-Gasior L, Hiszczyńska-Sawicka E (2009). Current status of toxoplasmosis vaccine development. *Expert Rev. Vaccines*. **8**: 791-808
- Lynfield R and Guerina NG (1997). Toxoplasmosis. *Pediatr. Rev.* **18**: 75
- Manger LD, Hehl AB and Boothroyd JC (1998). The surface of *Toxoplasma* tachyzoite is dominated by a family of glycosylphosphatidylinositol-anchored antigens related to SAG-I. *Infect. Immun.* **66**: 2237-2244.
- Martin F (2000). Congenital toxoplasmosis: Value of antenatal screening and current prenatal treatment. *TSMJ*. **1**:46-51
- Matowicka-Karna J, Dymicka-Piekarska V, Kemon H (2009). Does *Toxoplasma gondii* infection affect the levels of IgE and cytokines (IL-5, IL-6, IL-10, IL-12, and TNF-alpha)? *Clin. Dev. Immunol.* **37**: 46-96
- Mordue DG, Monroy F, La-Regina M, Dinardlo CA and Sibley LD (2001). Acute toxoplasmosis leads to lethal overproduction of Th 1 cytokines. *J. Immunol.* **167**:4574-4584.
- Mosmann TR and Moore KW (1991). The role of IL-10 in cross regulation at Th1 and Th2 responses. *Immunol. Parasitol. Today.* **12**: 49-53
- Okoh AEJ, Agbonlahor DE, Momoh M (1981). Toxoplasmosis in Nigeria: A serological survey *Trop. Anim. Health Prod.* **13**:137-143
- Onadeko MO, Joynson DH, Payne RA, Francis J (1996). The prevalence of toxoplasma antibodies in pregnant Nigerian women and the occurrence of stillbirth and congenital malformation. *Afr. J. Med. Medic. Sci.* **25**:331-334
- Pedrol E, Gonzalez Clement JM, Gantell JM, Mallolas J, Miro M and Graus F (1990). Central nervous system toxoplasmosis in AIDS patients: efficacy of intermittent maintenance therapy. *AIDS.* **4**: 511-517
- Peyron F, Wallon M, and Bernadoux C. (1996). Long term follow up of patients with congenital ocular toxoplasmosis. *N. Engl. J. Med.* **334**: 993-994.
- Peyron F, Lobry J, Muret K, Ferrandiz J, Gomez-Marin JE and Petersen E (2006). Serotyping of *Toxoplasma gondii* in pregnant women. Predominance of type II in the old world and type I and III in the new world. *Microb. Infect.* **8**: 2333-2340
- Pinon JM, Dumon G and Chemla C (2001). Strategy for diagnosis of congenital toxoplasmosis: evaluation of methods comparing mothers and newborns and standard methods of post-natal detection of immunoglobulin G, M and IgA antibodies *J. Clin. Microbiol.* **39**: 2267-2271.
- Prášil P (2009). Current options for the diagnosis and therapy of toxoplasmosis in HIV-negative patients. *Klin. Mikrobiol. Infekc. Lek.* **15** : 83-90
- Remington JS, Mcleod R and Desmonts G (1995). Toxoplasmosis. In: Remington J. S and Klein J. O. eds. *Infectious disease of the foetus and newborn.* Infant Philadelphia: W. B. Saunders Company. Pp: 140-267.
- Roberts F and Mcleod R (1999). Pathogenesis of toxoplasmic retinochoroiditis. *Parasitol. Today.* **15**: 51-57.
- Robert F, Gavnet MF, Anelle T, Raymond J, Tourte CT, and Dupouy CJ (1999). Value of prenatal diagnosis of congenital toxoplasmosis; retrospective study of 110 cases. *J. Clin. Microbiol.* **37**: 2893-2898.
- Rosso F, Les JT, Agudelo A, Villalobos C, Chaves JA, Tunubala GA, Messa A, Remington JS and Montoya JG (2008). Prevalence of Infection with *Toxoplasma gondii* among Pregnant Women in Cali, Colombia, South America. *Am. J. Trop. Med. Hyg.* **78**: 504-508.
- Robert-Gangneux F, Yera H, D'Herve D, Guiguen C (2009). Congenital toxoplasmosis after a preconceptional or periconceptional maternal infection. *Pediatr Infect. Dis. J.* **28**:660-661
- Rusiňáková Z, Raida L, Faber E, Tomková J, Bednaříková J, Indrák K, Novotný D (2009). Toxoplasmosis after immunosuppressive therapy - our experience. *Klin. Mikrobiol. Infekc. Lek.* **15**: 95-98.

Safadi MAP, Berezin EN, Farhat EK and Carvalho ES (2003). Clinical presentation and follow up of children with congenital toxoplasmosis in Brazil. *Brazilian J Infect Dis* **7**:325-331

Shaw SK, Hermanowski – Vosatka A, Shibahara T, McCommick BA, Parkos CA, Carlson SL, Ebert EA, Brenner MB and Madara JL (1998). Migration of intestinal intraepithelial lymphocytes into a polarized epithelial monolayer. *Am. J. Physiol.* **275**: 584-591

Sher A, Denkers EY and Gazzinelli RT (1995). Induction and regulation of host cell mediated immunity by *Toxoplasma gondii*. *Ciba Found Symp.* **195**: 95-104.

Shrittematter C, Lang W, Wiestter OD, Kleihues P (1992). The changing pattern of HIV associated cerebral toxoplasmosis. *Acta. Neuropathol.* **8**: 475-481.

Silveira C, Belfort R. Jr, Muccioli C, Abreu M. T. Martins M. C and Victoria C (2001). A follow up study of *Toxoplasma gondii* infection in southern Brazil. *Am. J. Opthamol.* **13**:351-354.

Singh S, Lodha R, Passi G. R and Bhan MK. (1998). Cholangitis due to congenital *Toxoplasma gondii* infection in an infant. *Indian J. Paediatr.* **65**:77-80.

Singh S (2003). Mother to child transmission and diagnosis of *Toxoplasma gondii* infection during pregnancy. *Indian J. Med. Microbiol.* **21**: 69-76.

Suzuki IA, Rosha RJ and Rossi CL (2001). Evaluation of serological markers for the

immunodiagnosis of acute acquire toxoplasmosis. *J. Med. Microbiol.* **50**: 62-70.

Torrey FE and Robert YH (2003). *Toxoplasma gondii* and Schizophrenia. *Emerg. Infect. Dis.* **9**:1375-1380.

Varella IS, Canti IC, Santos BR, Coppini AZ, Argondizzo LC, Tonin C, Wagner MB (2009). Prevalence of acute toxoplasmosis infection among 41,112 pregnant women and the mother-to-child transmission rate in a public hospital in South Brazil. *Mem Inst Oswaldo Cruz.* **104**: 383-388

Villena I, Chemla C, Quereux C, Dupony D, Leroux B, Foudrinier F and Pirion JM (1998). Prenatal diagnosis of congenital toxoplasmosis transmitted by an immunocompetent woman infected before conception. *Reims Toxoplasmosis group. Prenat. Diagn.* **18** :1079-1081.

Wan KL, Carrathers VB, Sibley LD and Ajoka JN (1997). Molecular characterization of an expressed sequence tag locus of *Toxoplasma gondii* Mic-2. *Mol. Biochem. Parasitol.* **84**: 203-214.