South Asian Journal of Parasitology

2(4): 1-10, 2019; Article no.SAJP.50588

Congenital Toxoplasmosis: Present and Future Challenges: A Review

Nataala U. Shehu[1*], Kumurya A. Sale[2], Kabiru Mohammed[1], Mauhammad K. Garba[1], Nura Bunza[1], Ahmed M. Ganau[1] and Ashcroft O. Fumilayo[1]

[1]Department of Medical Microbiology, School of Medical Laboratory Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria.
[2]Department of Medical Laboratory Science, Faculty of Allied Health Sciences, Bayero University, Kano, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. Authors NUS and KAS designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors KM and MKG managed the analyses of the study. Authors NB, AMG and AOF managed the literature searches. All authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. Somdet Srichairatanakool, Professor, Department of Biochemistry, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand.
Reviewers:
(1) Nitesh Mohan, Bareilly International University, India.
(2) Silke Anna Theresa Weber, Sao Paulo State University, Brazil.
Complete Peer review History: http://www.sdiarticle3.com/review-history/50588

Review Article

Received 20 June 2019
Accepted 30 August 2019
Published 07 September 2019

ABSTRACT

Recent findings shows that decrease of vertical transmission and clinical sequelae may be as result of screening and treatment for toxoplasmosis. Reduction of *T. gondii* infection is directly connected with early treatment. In this way, laboratory diagnostic techniques should direct for early identification of infants with congenital toxoplasmosis. Detecting the infection early and giving proper treatment immediately, may help reduce some of the severe health outcomes associated with the toxoplasmosis. Presently polymerase chain reaction (PCR) is the most commonly used and also the most accepted laboratory method employed for the diagnosis of Congenital Toxoplasmosis during gestation period. The gold standard for the diagnosis of Congenital Toxoplasmosis is the detection IgG antibody in the serum. In addition, in-depth epidemiological studies are needed to inform the design of regional strategies and to guide implementation of control programs involving both the medical and veterinary sectors.

**Corresponding author: E-mail: nataala03@yahoo.com;*

Keywords: Congenital toxoplasmosis; T. gondii; polymerase chain reaction; zoonotic parasite.

1. INTRODUCTION

Toxoplasma gondii belong the kingdom Protista and sub-kingdom protozoa. It is considered as a zoonotic parasite that can infect man and almost all warm blooded animals [1,2,3]. It is an intra-cellular parasite that causes toxoplasmosis [4,3]. *T. gondii* belongs to the kingdom protista sub-kingdom protozoa and phylum Apicomplexa, it was isolated in African rodent "*Ctenodactylus gundii*" in 1908 by Charles Nicolle (A French bacteriologist) and Louis Herbert Manceaux (A French parasitologist) at Pasteur institute, Tunis [5,3,6]. In the developed countries *T. gondii* is among the most widespread parasites [5,4,2]. Serological studies show that 10–90% of the world population has been exposed to *T. gondii* and may be carrying a latent infection. Infection rates may differ significantly from one country to another depending on environmental factors, socioeconomic status and geographic area [7,8,9]. From previous estimates France was shown to have the highest prevalence of people infected with *T. gondii* (84%) [6,7]. In Nigeria seroprevalence of human toxoplasmosis is estimated at 32% [9]. Mild, flu-like symptoms may occur during the first few days of exposure, even though infection with *T. gondii* produces no observable symptoms in healthy immuno-competent people [10,6,5]. This symptomless state of infection is known as a latent infection and is in most cases associated with numerous adverse or pathological behavioral changes in humans [5,6]. In many occasions, infants, HIV/AIDS, and other immunocompromised patients with weakened immunity, infection may result in a serious and fatal illness; *T. gondii* has been shown to interfere with the behavior of infected rats in a ways that increase the rats' chances of being preyed upon by felines [5,11,6]. Support for the "manipulation hypothesis" is shown in the studies of *T. gondii*-infected rats. The rats show a decreased aversion to cat urine [12,5,6]. Cats being the only hosts in which *T. gondii* can reproduce sexually to finish and start a new lifecycle, such behavioral manipulations are thought to be evolutionary adaptations that increase the parasite's reproductive success [5,12,6]. The rats are not afraid of the cat and may even be attracted to areas where cats live, and should the cat try to prey on them thy may be unable to escape. *T. gondii*–induced behavioral changes in rats is now known to occur through epigenetic re-modeling in neurons which govern the associated behaviors; it modifies epigenetic methylation to cause hypomethylation of arginine vasopressin-related genes in the medial amygdala resulting in the decrease predator aversion [6,12]. Histone lysine acetylation in cortical astrocytes is an example of another epigenetic mechanism employed by *T. gondii*. It has been observed that there is difference in aversion to cat urine between non-infected and infected humans [5,12]. Many studies have observed that behavioral or personality changes may occur in people infected *T. gondii* and infection with this parasite has recently been connected with a number of disorders particularly schizophrenia and bipolar disorder diseases [6]. The most common target group of *T. gondii* are people with HIV/AIDS, cancer, organ transplant and fetus bearing pregnant women where the infection develops toxoplasmic encephalitis, hydrocephalus, microcephalus, myocarditis, chorioretinitis and abnormal fetal brain development or stillbirths respectively [5]. Other studies have found schizophrenia, depression, anxiety and other mental diseases are more common in people with toxoplasmosis, and there is also evidence to suggest infection by the parasite is linked to more extroverted, aggressive and risk-taking behavior [12,6].

2. LIFE CYCLE OF *Toxoplasma gondii*

Infection by the intracellular apicomplexan parasite *Taxoplasma gondii* affects an estimated 25–30% of humans worldwide making this zoonotic parasite one of the most widespread human pathogens in the world [6,3]. When a cat, (definitive host) consumes a rodent (containing bradyzoites), the bradyzoites changes into merozoites inside intestinal epithelial cells of the gut [13,5]. After a brief period of rapid population increase in the intestinal epithelium, merozoites changes into the noninfectious sexual forms of the parasite to undergo sexual reproduction, finally resulting in a zygote-containing oocysts [3,6]. Infected felids excrete up to several hundred million environmentally resistant oocysts with their feces, which can infect any warm-blooded animal upon ingestion [5]. *T. gondii* reproduces asexually via two distinct life cycle stages, the fast growing tachyzoite and the slower reproducing bradyzoite stage [13,3]. The latter forms cysts in various host tissues, which may be consumed by carnivores or omnivores. Cysts usually vary in size between five (5) and fifty (50) μm in diameter, (50 μm is about two-

thirds of the width of an average hair of human) [5]. Following ingestion, bradyzoites are released from the tissue and transformed into tachyzoites which are actively dividing and infect other host cells [11,8]. In the host cells, the tachyzoites multiply inside specialized vacuoles (this vacuole is called parasitophorous vacuoles) created as the parasitic enter into the host cell [5,8].

Tachyzoites which are the actively dividing forms of the parasite multiply inside this parasitoporous vacuole until the host cell is killed and ruptured, the released tachyzoites spread via the bloodstream to various organs and tissues of the body, including the heart and brain [8,3]. Man may acquire the infection by ingesting of undercooked or uncooked meat containing *T. gondii* cysts, ingestion of oocysts from contaminated hands, food, soil, or water contaminated with feline feaces, organ transplantation or blood transfusion from infected donors, trans-placental transmission from an infected mother to fetus etc. [14,15,5,4]. There are two major ways of transmitting *T. gondii* to humans these are oral and congenital [5,12,13]. Whether the tissue cyst or oocyst is ingested, it resulted in the rupture of the cyst wall which releases sporozoites that invade the intestinal epithelial cells, from there it disseminate throughout the body, and multiply intracellularly [16,5]. The infected host cells are killed and ruptured releasing tachyzoites, which invade adjacent cells and continue the process [17,14,18]. The tachyzoites are challenged by the host's immune response and this result in the transformation into bradyzoites and form tissue cysts, most commonly in skeletal, muscle, myocardium, and brain etc [14,5]. The cysts may remain as long as the host lives [5]. In a situation whereby the host become immunocompromised clinical disease may occur if the cysts bust, releasing the parasites [5]. When a cat or any member of the feline family ingests food or water

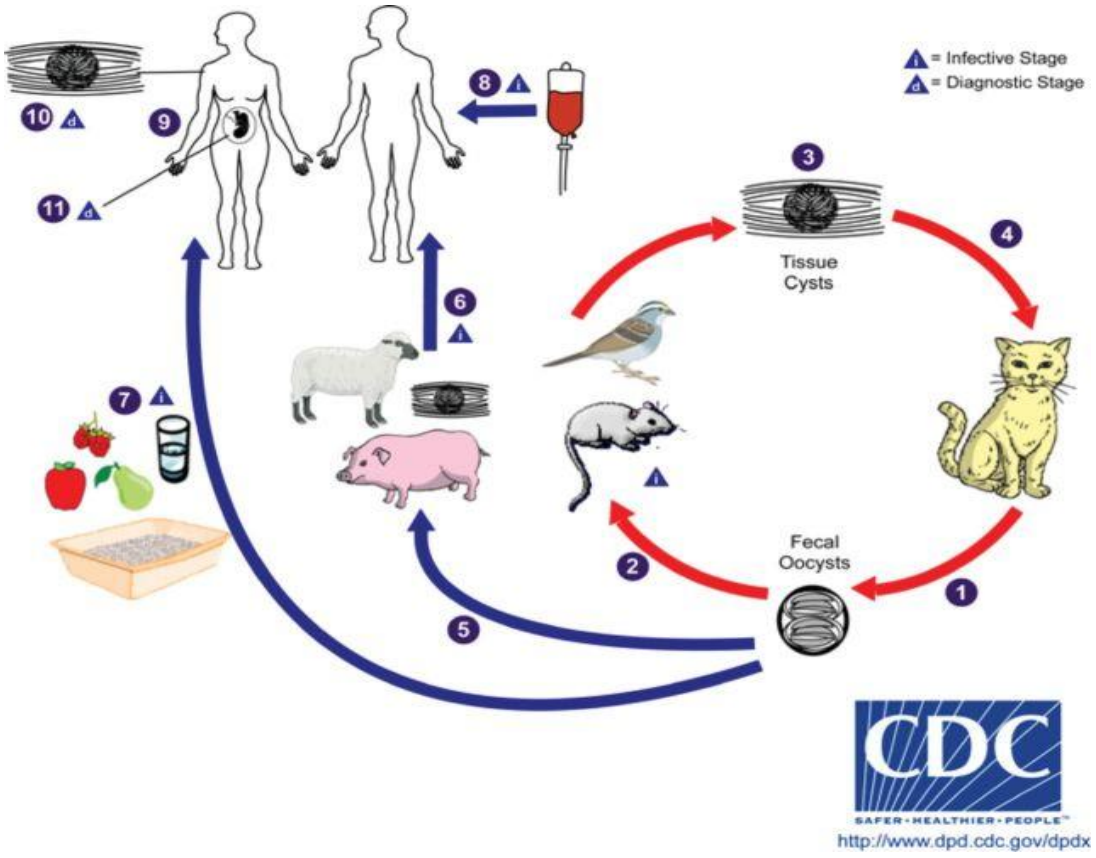

Fig. 1. Life cycle of *Toxoplasma gondi*
Source: http//www.dpd.cdc.gov/dpdx

contaminated with the oocyst or feed on an infected rodent (containing bradyzoite cyst), the sexual cycle is initiated [7]. The bradyzoitesn undergo changes to form the sexual stages which finally result in the shedding of oocyst in the cat feaces [8]. The oocyst sporulates in the soil for five days and become infective and can survive up to one year in the environment [8,5,19]. Any warm blooded animals that ingest this cyst become a host for the asexual life cycle [20,15,4]. Upon ingestion of tissue cyst in raw undercooked meat from an infected host, intestinal epithelium of the host become infected with bradyzoites and differentiate back to tachyzoites to complete the life cycle [16,4,19].

3. CONGENITAL TRANSMISSION

Infection of the fetus occurs in most cases after primary infection of a pregnant woman [5]. The incidence of congenital toxoplasmosis varies with the trimester during which maternal infection was acquired. For women that are not treated, transmission rate is approximately 25 percent in the first trimester, 54 percent in the second trimester, and up to 65 percent in the third trimester [5]. Although the mother will generally not notice any symptoms, the infection may spread to the baby before birth or in the process of labour and delivery [21,22,5]. Babies with toxoplasmosis are often born too early and can have a variety of health problems affecting organs like the ears, skin, eyes, nervous system etc. [5, 16]. For some babies with toxoplasmosis, detecting the infection early and beginning proper treatment immediately may help prevent some of the severe health outcomes associated with the condition [5,8]. Although the exact mechanism by which the parasite passes across the human placenta is not well understood, recent research may offer new insights [23,24]. Studies of the placenta indicate that extra-villous trophoblasts (EVT) that attach the placenta to the uterus are more vulnerable to infection than the syncytiotrophoblasts that are bathed in maternal blood [20,5,25]. Many studies in animals indicated that initial infection occurs in the uterus of an infected mother [5]. In this way, it is possible that after primary infection a pregnant mother becomes parasitemic, resulting in intracellular infection of the uterus, which then gradually results in EVT infection, as the tachyzoites move from one cell to another, with eventual infection of the fetus in the uterus [5]. There is possibility that direct movement of actively dividing tachyzoite infected maternal leukocytes across the placenta play a role in the infection of the fetus [26,24]. Congenital toxoplasmosis is one of the most important manifestation of infection apart from those of immune- compromise host, it result from the vertical transmission of *T. gondii* across the placenter from a parasitemic mother to her offspring [5,22]. The extent of disease depends on the gestational age at the time of transmission [27,22]. Some of the disabilities associated with this condition are choriorhitinitis, hydrocephalus, microcephalus, epilepsy etc. Most of these conditions can be present even when the congenital infection is asymptomatic [9,22].

The infected young infant/newborn and fetus are at risk of infection-associated complications, such as choriorhitinitis that can occur in adulthood [6,5,22]. HIV/AIDS patient are at increased risk for severe disease because of the defect in cellular immunity [21,12]. Congenital toxoplasmosis is a disease that can be prevented and controlled [28,5,22].

4. PATHOGENESIS

Clinical manifestation of toxoplasmosis in humans is in most cases limited to either immune-compromised patient or to congenital disease resulting from an acute infection of the mother [19,4]. *T. gondii* infction can be divided into 4 groups: (1) acquired in immunocompetent patient; (2) acquired or reactivated in immunodeficient patient; (3) Ocular, and (4) Congenital. For each group diagnosis and treatment may be different [5]. Acquired infection with *T. gondii* in immunocompetent patients is in most cases without symptoms [5,4]. Only very few patients with acute infection develop cervical lymphadenopathy or a flu-like illness [29,1]. The clinical symptoms are benign and self-limited; in most cases symptoms disappear within few weeks [5,24]. Data from recent studies have suggested an association between *T. gondii* infection and various abnormalities such as schizophrenia, microcephalus, hydrocephalus Alzheimer disease, and sometimes even suicide [5]. These findings are interesting but require further study to validate.

Immunocompromise patients most of the time have central nervous system (CNS) disorder and may also have myocarditis or pneumonitis etc. [18,8]. Reactivation of chronic infection in patients with acquired immune deficiency syndrome (AIDS) may result in toxoplasmic encephalitis the most common cause of intracerebral mass lesions [6]. *Taxoplasma*

gondii infection in patients receiving treatment with immunosuppressive drugs may be due to newly acquired, reactivated latent infection or Ocular toxoplasmosis. In USA an important cause of chorioretinitis may be congenital or acquired infections [5]. After congenital infection patients can be symptomless until the second or third decade of life, when lesions appear in the eye due to cyst rupture releasing large number of tachyzoites [5,17]. Eye infection is more often bilateral in congenitally infected persons than in those with acute acquired *T. gondii* infection [5]. An ongoing research in understanding ocular toxoplasmosis is shedding more light in the interaction of human immunity, timing of infection and parasite genotype [25,5]. Congenital infection of *T. gondii* has a very wide range of clinical manifestations, but it is subclinical in many of infected newborns [22,24,30]. The extent of clinical disease in congenitally infected infants is related inversely to the gestational period at the time of primary maternal infection—with first-trimester maternal infection resulting in more severe manifestations [24,30,5]. If the clinical condition is apparent, it may appear like other disease conditions of the newborn. In some cases, abortion, premature birth, or stillbirth may result. Involvement of the CNS is a common condition associated with congenital *T. gondii* infection [31,5,32]. The presence of abnormalities such as chorioretinitis, intracranial calcifications, microcephalus and hydrocephalus are common features in congenital *T. gondii* infection [5]. Hydrocephalus or microcephaly, hepatosplenomegaly, jaundice, convulsions, cerebral calcifications, and abnormal cerebrospinal fluid (CSF) are among the identifying features of severe congenital toxoplasmosis [33,5]. Other rare clinical findings include rash, myocarditis, pneumonitis and respiratory distress, hearing defects, an erythroblastosis-like condition, thrombo-cytopenia, lymphocytosis, monocytosis, and nephrotic syndrome [34, 24, 5]. Neonate children that are not having overt disease may escape serious sequelae of the infection; however, in much cases large number may develop chorioretinitis, strabismus, blindness, hydrocephalus, cerebral calcifications, developmental retardation, epilepsy, or deafness later in their life [5,29]. Current treatment is directed against the actively dividing tachyzoite form of *T gondii*. Newer drugs such as azithromycin, atovoquone, etc are areas requiring further research for optimal treatment regiment with activity against the various stages of the parasite. It is used a months after delivery and can significantly reduce subsequent neurologic damage in children infected with *T. gondii* [5]. The extent of congenital infections depends on the period of pregnancy when the acute infection take place, abortions or neurological abnormalities such as loss of sight and mental retardation can occur [5]. In the last twenty years, high increase in the number of immuno-suppressed persons has been observed and thus a corresponding increase in severe toxoplasmosis [4]. Within this latter patient group, *T. gondii* infection is a common cause of intra-cerebral focal lesions resulting in toxoplasmic encephalitis [34,4]. Toxoplasmic encephalitis can be fatal if it is allowed to go untreated, thus, this disease represents a serious concern in the HIV/AIDS patients [35,4]. Although the current drugs sulfonamide and pyrimethamine that are used for the treatment of toxoplasmosis will effectively kill the actively dividing tachyzoite stage, it does not have any effect on the chronic bradyzoite stage; therefore long-term therapy is requared [4,26]. The toxic side effects of many of these drugs, together with their inability to remove the infection completely, makes it clear that there is need for safer and more effective treatments options [5,4]. In recent studies of Toxoplasmosis, researchers have discovered that differences observed in reactivation and extent of the disease can probably be explained by different genotypes of *T gondii*, of which there are three in different parts of the world. These findings are important because they can be used to explain conflicting reports from different areas of the world on the public health importance and treatment for congenital disease [5]. There is need for more research to give detail role of *T gondii* genotypes and their interaction with human innate immunity, especially in the fetus and newborn infant. Study on transmission across the human placenta indicated a trend towards increased transmission ability by one of the genotype; although the differences were not statistically significant [5].

Early in the infection, *T. gondii* stimulates production of IL-2 and Interferon- γ (IFN-γ) by the innate immune system [5,6,28]. Continuous IFN-γ production is essential for control of both acute and chronic Toxoplasmoses [22,6,17]. These two cytokines that are produced stimulate a CD4+ and CD8+ T-cell mediated immune response [5,23]. T-cells play a key role in immunity against *Toxoplasma* infection. *Toxoplasma* antigens are recognized by T-cells when presented by the body's own Major Histocompatibility Complex (MHC) molecules [6,36,25]. MHC molecule

differs significantly in their genetic sequence from one individual to another, which is why these molecules are involved in transplant rejection [5]. Individuals carrying particular genetic sequences of MHC molecules are much more likely to be susceptible to *Toxoplasma* infection than others [6,25]. In a study of >1600 individuals it was found that *Toxoplasma* infection was particularly more common among people who expressed certain MHC alleles (HLA-B*08:01, HLA-C*04:01, HLA-DRB 03:01, HLA-DQA*05:01 and HLA-DQB*02:01) [7]. IL-12 which is produced during *T. gondii* infection activate natural killer (NK) [6]. *T. gondii* scavenges tryptophan; an essential amino acid for its survival from host cells. IFN-γ stimulate the activation of indole-amine-2, 3-dioxygenase (IDO) and tryptophan-2,3 dioxygenase (TDO), the two enzymes produced are responsible for the degradation of tryptophan [6,7]. Pressure from the immune defenses of the host leads to the formation of cysts which are eventually deposited in the muscles and in the brain tissure of the hosts [37,21]. The interferon-γ-mediated activation of IDO and TDO is believed to be an evolutionary adaptation that serves to starve the parasite; on the other hand it can also result in depletion of tryptophan in the brain tissues of the host [5,24]. Tryptophan is degraded by IDO and TDO to N-formylkynurenine and addition of L-kynurenine is capable of inducing depressive-like behaviour in mice [6,5,7]. *T. gondii* infection has been associated to increase levels of kynurenic acid (KYNA) in the brains tissues of infected mice and KYNA has also been associated to increase in the brain tissues of schizophrenic individuals [11]. Low levels of tryptophan and serotonin in the brain were already associated to depression [5,6].

5. EPIDEMIOLOGY

Available data on serologic prevalence shows that *T. gondii* infection is one of the most common infections of humans throughout the world, and prevalence increases with age [37, 19,5]. Because of environmental factors affecting the oocysts survival, infection is more common in hot climates and at lower altitudes than in cold climates and mountainous areas [29,5]. Differences in nature of exposure can also lead to variations in prevalence. Analysis of National Health and Nutrition Examination and Survey (NHANES) data showed *T. gondii* seroprevalence had declined in United State-born persons 12–49 years old from 14.1% in 1988–1994 to 9.0% in 1999–2004 [5]. The prevalence of congenital *T. gondii* infection depends upon the number of women becoming pregnant without vaccination and the level of exposure to *Toxoplasma* during pregnancy. Congenital toxoplasmosis in the United States has been estimated to range from 1 in 3000 to 1 in 10 000 live births. In 2014, 42 confirmed congenital toxoplasmosis cases were reported by 20 European Union/EEA countries [6,5]. This represents a fivefold decrease compared with 2013, which is mainly due to missing data from France [6]. Excluding the French congenital toxoplasmosis data, the number of cases reported in 2014 is comparable to the annual number of cases reported between 2010 and 2014, i.e. an average of 34 cases/year. Two countries reported the majority of cases in 2014, namely Poland (48%) and the United Kingdom (26%) [34]. Prevalence rate of *T. gondii* nfection in India has been reported as 22.4% (8.8-37.3%) The overall IgM positivity was reported as of 1.43% [1]. Approximate estimate have shown that between 56,737 and 176,882 children per anum are born in India with a possible risk of congenital *T. gondii* infection [1,29]. The most common method used in the diagnosis of congenital toxoplasmosis is by serological method. Some other methods used are isolation of parasite by culture and molecular techniques. *T. gondii* infection is treatable and transplacental transmission can be minimize or prevented by treatment with spiramycin, which concentrates in the placenta. In a situation where the infection has done any damage to the developing fetus or the parasite has already passed the placenta, spiramycin cannot reverse the damage. Prevention remains the best option [1]. In Morocco the seroprevalence of *T. gondii* in pregnant women ranged between 36.7% and 62.1%, between 2007 and 2017 [3]. As a novel diagnostic tool, the chemiluminescent microparticle immunoassay (CMIA) was used for *T. gondii* antibodies detection among pregnant women in Fes city [3]. Among the risk factors, age was the most commonly reported factor in these studies and the overall conclusion is that the prevalence of *Toxoplasma* infection increases with age [37,26,18]. Infection rates also varied according to the locality; reaching 50.6% in Rabat which is higher than 43.3% in Nador (North East), 42.6% in Tetouan (North) and 36.7% in Kenitra (North West) [3]. The authors attributed this difference to the temperate climate of Rabat city, which maintains the biological cycle of *T. gondii* (rapid and complete sporulation). Regular contact with the land (soil, gardening and agricultural activities) was

retained as a major risk for *T. gondii* infection in Rabat city [3,25]. In one study conducted in Rabat and concerning pregnant women, school level and knowledge of toxoplasmosis modes transmission were found to be risk factors ($p < 0.01$), while the consumption of raw meat, contact with cats, and level of hygiene were not significant. Results of toxoplasmosis epidemiological surveys in animals and humans in South-West, North-West, North-East and North-Central Zones of Nigeria have been reported with greater impact on the health of pregnant women and HIV-infected individuals [9,36]. Meanwhile, studies in states within the South-South and South-East Zones are relatively scanty or non-existent. Overall, the seroprevalence of human toxoplasmosis in Nigeria is estimated at 32% with the following reports for North-West (32%), North-East (22%), North-Central (24%) and South-West (37%) [9]. Information on the genetic diversity of isolates of *T. gondii* in man and animals including the role of the environment in transmission and maintenance of the disease are highly needed [9,5].

6. DIAGNOSIS

Diagnosis of Congenital *T. gondii* infection in the developing fetus during gestation; the presence of the parasite in amniotic fluid can be diagnose using DNA amplification, isolation of the organism using culture medium, antigen staining, microscopy [16]. Isolation of the organism using culture medium is diagnostic of Congenital *T. gondii* infection [16]. The laboratory technique that is widely accepted and commonly used for the diagnosis of Congenital *T. gondii* infection during gestation is PCR using amniotic fluid, and a positive result is diagnostic of Congenital Toxoplasmosis [24,16]. The gold standard for the diagnosis of *T. gondii* infection in the postnatal period is the detection of *Toxoplasma* IgG by at least one year after birth [13,16]. On the other hand the best way to rule out the diagnosis is the decrease of *Toxoplasma* IgG titers until its disappearance at or before one year in the absence of treatment [30,31,16]. Some of the diagnostic methods employed for *Taxoplasma gondi* include the following: In 1948, Sabin and Feldman develop a serological assay called the dye test for conducting serological diagnosis of toxoplasmosis [8,32,33]. Immunohistochemical staining of *Taxoplasma* with fluorescent or any type of labelled *T. gondii* antisera can help in the diagnosis of the infection [7]. In women it is based on serology by detecting IgG and IgM antibodies [35,16]. The bradyzoites of *T. gondii* cysts in the tissues are spherical in shape, aseptate, and can be stained with a periodic acid Schiff (PAS) staining technique [11]. Diagnosis can be achieved by finding *T. gondii* in tissues of the host removed by biopsy or at necropsy [11,36]. A quick diagnosis can be achieved by microscopic examination of impression smears from lesions in the host [11,6]. *T. gondii* can be diagnosed by means of serology, culture based methods using RPMI 1640 medium, mouse assay and PCR [13]. It is very important to confirm whether the mother is immuno-compromised or immunocompetent and also if she belongs to any of the following three groups: (i) Has never been infected with *Toxoplasma* and confirmed to be seronegative a month after given birth, there is no risk for Congenital infection with *T. gondii*), (ii) latent infection—mother acquired her infection before gestation (there is no risk for Congenital *Taxoplasma* infection unless if the mother immunocompromised), or (iii) acutely infected- the infection is acquired during gestation or within 3 months before gestation (high risk for Congenital taxoplasmosis) [16]. For third group, it is important to estimate the month during which maternal infection was acquired and whether the mother has received any anti-*Toxoplasma* treatment and the type of drug since the sensitivity and interpretation of laboratory test result can be seriously affected by these variables [16]. It has been observed that, babies born by mothers who acquired their infection early in gestation and received treatment during gestation have lower sensitivity of serological test than in those born to mothers who acquired their infection late in gestation and did not receive treatment [16]. Detail information about the clinical signs in the fetus and newborn is important and can be helpful in the interpretation and recommendations to be given regarding intervals for follow-up tests after birth or in some cases indication for additional tests e.g., ELISA or *Toxoplasma* PCR [12,38,16]. Furthermore, brain imaging studies and retinal exams can also exhibit findings that are highly suggestive of toxoplasmosis, and in the absence of alternative etiologies and proper clinical context, they can be diagnostic [16]. The laboratory diagnosis of congenital toxoplasmosis has benefited from many different principles and methods. Future research should overcome the problem of cost and feasibility of detection of antibodies, DNA, and live parasite in different platforms and body compartments. Example, simultaneous detection of multiple analytes in the same assay offers a better option for detection of *Toxoplasma* IgG,

IgM, and IgA and of antibodies against other pathogens with the capacity to cause congenital infection. The use of platforms with multiplex capacities can address cost, with the additional benefit that they may be extended to other infections [16].

7. TREATMENT AND PROGNOSIS

Many people with toxoplasmosis will have an excellent outcome with no significant problems and treatment is often unnecessary [38,19,39]. An infected fetus or infant has a prognosis that may range from good to poor, depending on when in development they become infected, how rapidly the disease progresses and is diagnosed, and the response to treatment [39,19]. While on the other hand, the prognosis is usually poor if the fetus is infected in the first trimester; many such fetuses die or develop severe physical and mental problems seen at birth. Immuno-compromised individuals have a good to poor prognosis, depending on how quickly the diagnosis is made and how well the patient responds to treatment. For example, if encephalitis develops due to toxoplasmosis in a patient with HIV, the prognosis can be good if the patient responds to treatment, but treatment usually needs to be continued for life [19]. Fetuses and immunocompromised individuals are at particularly high risk for severe sequelae and even death. Newborns with acute congenital toxoplasmosis often die in the first month of life. Infection acquired postnatally is usually much less severe [22].

8. PREVENTION AND CONTROL

The fetus can be prevented from infection by given an infected mother spiramycin (a mycrolide antibiotic that does not cross the placenta [8]. Reduce Risk from Food by cooking food to safe temperatures. The internal temperature of cooked meat should be measured using food thermometer and ensured that it is at least 74°C [26]. Fruits and vegetables should be thoroughly wash before eating. Wash thoroughly with clean soap and water all cutting boards, dishes, counters, utensils, and hands before and after contact with raw meat, poultry, seafood etc. [5]. AIDS patients who have just recovered from acute infection with *T. gondii* are at high risk of future occurrence, because the latent stage of infection may be reactivated. To minimize this occurrence, an AIDS patient must start a regimen of preventive drugs [40]. The regiment of this drug must be continued as long as immune system remains weakened [5,7]. Cats that are infected pass out oocysts only for a few weeks after ingesting the parasites and younger cats are more likely to pass on the infection than older ones [5,6]. Some suggestions on reducing the risk of becoming infected include the following; Keeping cats indoors whenever possible [23]. You should not allow your cat to hunt and eat birds, rats etc. in the wild. Cats should be fed canned or dry foods. Avoid giving raw meat to your cat. Oocysts pass out in cat feaces take at least one day to become infective therefore, disposing of cat litter daily will go a long way in reducing the chances of infection by oocysts present in the litter [6,5]. Infectious oocysts from cat feces can spread and survive in the environment for up to a year, so anybody handling cat or cat litter should wear hand gloves. [6]. Furthermore, Pregnant and immunocompromised individual are at higher risk of becoming infected or transmitting the infection to their fetus, because of this, they should never change or handle their cat litter boxes. As mentioned earlier, cats should be kept indoors and fed only canned, dry, or well-cooked table foods that has little or no risk of carrying oocysts [6].

9. CONCLUSION

Congenital *T. gondii* infection is a disease that can be treated and prevented [5]. There should be a better treatment options available than what is obtainable now both for prevention of transmission from an infected mother to her fetus and for the treatment of congenitally infected children [5]. Many researches carried out on plants extract have shown activity against parasites related to *T. gondii,* is it time to seriously consider extending this research to *T. gondii*. There is need to organize a universal screening of pregnant women in order to diagnose those who are infected. A sound knowledge of the epidemiology is required in order to organize such a screening. More can be done to improve food safety. Perhaps now the time has really come for us to address the issue of congenital toxoplasmosis once and for all. Having better impact data would make it easier to convince decision makers to invest in toxoplasmosis control and prevention. In addition, more in-depth epidemiological studies are needed to inform the design of regional strategies and to guide implementation of control programs involving both the medical and veterinary sectors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Sarman S. Congenital toxoplasmosis: Clinical features, outcomes, treatment and prevention. Tropical parasitology. 2016;6(2): 113-122.
   DOI: 10.4103/2229-5070.190813
2. Hunter CA, Sibley LD. Modulation of innate immunity by *Toxoplasma gondii* virulence effectors. Nat. Rev. Microbiol. 2012;10: 766–778.
3. Mariem R, Safa A, Yosra A, Mohamed AB. Ouada A, et al. *Toxoplasma gondii* infection and toxoplasmosis in North Africa: A review. Parasite. 2019;26(2):153-158.
4. Michael WB, John CB. Life cycle of *Taxoplasma gondii* Microbiol Mol Biol Rev 2000;64(3):607-623.
5. James BM. Congenital toxoplasmosis. Journal of the Pediatric Infectious Diseases Society. 2014;3(1):S30-S35.
   DOI: 10.1093/jpids/piu077
6. Available:https://en.wikipedia.org/wiki/Toxoplasma_gondii
7. Dubey JP, Hill DE, Rozeboom DW, Rajendrana C, Choudharya S, et al. High prevalence and genotypes of *Toxoplasma gondii* isolated from organic pigs in northern USA. Vet. Parasitol. 2012;188: 14–18.
   DOI: 10.1016/j.vetpar.2012.03.008
8. Taibur R, Atiqur R, Sajib C. Infection of *Taxoplasma gondiii* in human and livestock animals: An emerging silent threat for Bangladesh, Open Journal of Medical Microbiology. 2018;8(3):109-117.
9. Ohiolei JA, Isaac C. Toxoplasmosis in Nigeria: The story so far (1950-2016) Folia Parasitologica. 2016;63:30-37.
10. Villard O, Cimon B, Olliver CL, Fricker-Hidalgo H, Godineau N, Houze S, Paris L, Pellaoux H, et al. Serological diagnosis of *T. gondii.* Infect. Immun. 2015;6(4):623-627.
11. Berdoy M, Webster JP, Macdonald DW. Fatal attraction in rats infected with *T. gondii*. Proceeding of the Royal Society. 2000; 267;(1452):1591-1594.
    DOI: 10.1098/rspb.2000.1182.PMC1690701
    [PMID11007336]
12. Boothrovd, Robert MS. Behavioral changes induced by *Toxoplasma* infection of rodents are highly specific to aversion of cat odors. 2007;104(15):6442-7447.
    DOI: 10.1073/Proc.nati. Acad Sci USA
13. Harker KS, Ueno N, Lodoen MB. *Toxoplasma gondii* dissemination: A parasite's journey through the infected host. Parasite Immunol. 2015;37:141–149.
14. Tosh KW, Mittereder L, Bonne-Annee S, Hieny S, Nutman TB, Singer SM, et al. The IL-12 response of primary human dendritic cells and monocytes to *Toxoplasma gondii* is stimulated by phagocytosis of live parasites rather than host cell invasion. J. Immunol. 2016;196:345–356.
    DOI: 10.4049/jimmunol.1501558
15. Gazzinelli RT, Mendonça-Neto R, Lilue J, Howard J, Sher A. Innate resistance against *Toxoplasma gondii*: An evolutionary tale of mice, cats and men. Cell Host Microbe. 2014;15:132–138.
16. Christelle P, Jose GM. Laboratory diagnosis of congenital toxoplasmosis. Journal of Clinical Microbiology. 2016;5(3):732-739.
    DOI: 10.1128/JCM.00487-16
17. Blader IJ, Coleman BI, Chen CT, Gubbels MJ. Lytic cycle of *Toxoplasma gondii*: 15 years later. Annu. Rev. Microbiol. 2015; 69:463–485.
18. Fleckenstein MC, Reese ML, Könen-Waisman S, Boothroyd JC, Howard JC and Steinfeldt T. A *Toxoplasma gondii* pseudokinase inhibits host IRG resistance proteins; 2012.
19. Available:https://www.betterhealth.vic.gov.au
20. Estefania DB, Benjamin H, Benedikt TF, Christian K, Susanne H, Frank S. From entry to early dissemination- *Taxoplasma gondiii's* initial encounter with its Host. Frontiers Cellular Infection Microbiology. 2019;8(5):315-318.
21. Prusa AR, Kasper DC, Pollak A, Gleiss A, Waldhoer T, Hayde M. The Austrian Toxoplasmosis Register, 1992–2008. Clin Infect Dis. 2015;60(2):143-147.
22. Available:https://emedicine.medscape.com/article/1000028-overview
23. Jennes M, De Craeye S, Devriendt B, Dierick K, Dorny P, Cox E. Strain- and dose-dependent reduction of *Toxoplasma gondii* burden in pigs is associated with interferon-gamma production by CD8(+) lymphocytes in a heterologous challenge model. Front. Cell. Infect. Microbiol. 2017; 7:232.

24. Robbins JR, Zeldovich VB, Poukchanski A. Tissue barriers of the human placenta to infection with *Toxoplasma gondii.* Infect Immun. 2011;80:418–28.
25. Fritz HM, Bowyer PW, Bogyo M, Conrad PA, Boothroyd JC. Proteomic analysis of fractionated *Toxoplasma oocysts* reveals clues to their environmental resistance. Plos One. 2012;7:(9)55-59.
DOI: 10.1371/journal.pone.0029955
26. Available:https//healthjade.net/toxoplasmosis
27. Yarovinsky F. Innate immunity to *Toxoplasma gondii* infection. Nat. Rev. Immunol. 2014;14:109–121.
DOI: 10.1038/nri3598
28. Foureau DM, Mielcarz DW, Menard LC, Schulthess J, Werts C, Vasseur V. et al. TLR9-dependent induction of intestinal alpha-defensins by *Toxoplasma gondii*. Journal of. Immunology. 2010;184:7022–7029.
29. Available:https//healthjade.net/toxoplasmosis
30. Sher A, Tosh K, Jankovic D. Innate recognition of *Taxoplasma gondii* in humans involves a mechanism distinct from that utilized by rodents. Cell. Mol. Immunol. 2017;14:36–42.
DOI: 10.1038/cmi.2016.12
31. Dunay IR, Diefenbach A. Group 1 innate lymphoid cells in *Toxoplasma gondii* infection. Parasite Immunol. 2018;40(12): 516-521.
DOI: 10.1111/pim.12516
32. Available:https://medlineplus.gov/ency/article/001360.htm
33. Weidner JM, Barragan A. Tightly regulated migratory subversion of immune cells promotes the dissemination of *Toxoplasma gondii*. Int. J. Parasitol. 2014;4:85–90.
DOI: 10.1016/j.ijpara.2013.09.006
34. Cohen SB, Denkers EY. The gut mucosal immune response to *Toxoplasma gondii*. Parasite Immunol. 2015;37:108–117.
35. Klun I, Djurkovic-Djakovic O, Katic-Radivojevic S, Nikolic' A. Cross-sectional survey on *Toxoplasma gondii* infection in cattle, sheep and pigs in Serbia: seroprevalence and risk factors. Vet Parasitol. 2006;135:121–131.
DOI: 10.1016/j.vetpar.2005.08.010
36. Okewole EA. Seroprevalence of antibodies to *Toxoplama gondii* in some food and companion animals in the southwest Nigeria. Folia Vet. 2007;51(3–4):113–117.
37. Nau J, Eller SK, Wenning J, Spekker-Bosker KH, Schroten H, Schwerk C, et al. Experimental porcine *Toxoplasma gondii* infection as a representative model for human toxoplasmosis. Mediators Inflamm. 2017;3260289.
DOI: 10.1155/2017/3260289
38. Venturini MC, Bacigalupe D, Venturini L, Rambeaud M, Basso W, Unzaga JM, Perfumo CJ. Seropresvalence of *Toxoplasma gondii* in sows from slaughterhouses and in pigs from an indoor and outdoor farm in Argentina. Vet Parasitol. 2004;124:161–165.
DOI: 10.1016/j.vetpar.2004.07.003
39. Halsby K, Guy E, Said B, Francis J, O'Connor C, Kirkbride H, et al. Enhanced surveillance for toxoplasmosis in England and Wales, 2008–2012. Epidemiol Infect. 2014;142(8):1653-60.
40. Available:https://aids-stop.com/what-treatmen-are-there-for-aids-under-eyes/

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle3.com/review-history/50588