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AN OVERVIEW OF CONGENITAL TOXOPLASMOSIS: CLINICAL FEATURES, DIAGNOSIS, TREATMENT AND PREVENTION

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Abstract

Toxoplasmosis is a zoonotic protozoan disease results from infection with *Toxoplasma gondii*, one of the worldwide zoological and geographical distribution. *T. gondii* multiples sexually in the cat family (definitive host) and infects all warm-blooded animals, including humans (intermediate host) where it multiplies asexually. Transmission occurs by ingestion of raw or partly cooked meat, especially pork, lamb, or venison containing cysts, mainly in countries where undercooked meat is traditionally eaten. Also, cysts may also be ingested during hand-to-mouth contact after handling undercooked meat, or from using knives, utensils, or cutting boards contaminated by raw meat. Drinking water contaminated with *Toxoplasma* cysts. Also, receiving an infected organ transplantation or blood transfusion, or nosocomial (needle-stick injury) was reported. Ingestion of oocysts dropped with cat feces, through hand-to-mouth contact after gardening, cleaning a cat's litter box, contact with children's sandpits, or touching anything that came into contact with cat feces. Also, congenital toxoplasmosis or mother-to-child transmission do occurs during pregnancy. For infants born to infected mothers and for people with weakened immune systems, toxoplasmosis may cause serious complications.The clinical features, diagnosis and prevention of congenital toxoplasmosis in infants and children are reviewed here

Key words: Congenital toxoplasmosis, Complications, Diagnosis, Treatment, Recommendations

Introduction

Toxoplasma gondii is a ubiquitous protozoan parasite that infects animals and humans. Toxoplasmosis infection typically is asymptomatic in immunocompetent hosts (Koshy and Cabral, 2014). However, serious disease can occur, most frequently in the setting of immunosuppression or congenital infection. The fetus, newborn, and young infant with congenital *Toxoplasma* infection are at risk of infection-associated complications, particularly retinal disease that can occur into adulthood (Crosson *et al*, 2015).

Congenital toxoplasmosis is caused by *T. gondii*; an intracellular protozoan parasite with a unique biphasic life cycle consists of a sexual cycle (in felines) and an asexual cycle (all other animals and human). Cats acquire the infection by ingesting oocysts in soil or tissue cysts from small prey. Replication occurs in the intestine of the cat, and oocysts are formed, excreted, and become infectious after 24 hours (Dubey, 2009). During the primary infection, the cat can shed millions of oocysts daily for up to three weeks. Humans who come in contact with cat feces containing *Toxoplasma* oocysts may inadvertently ingest contaminated material, and the asexual phase of *Toxoplasma* replication begins. Oocysts rupture to release sporozoites that divide and become tachyzoites, which are characteristic of the acute stage of infection. Tachyzoites spread throughout the body via the bloodstream and lymphatics. With an adequate immune response, the tachyzoites are sequestered in tissue cysts and form bradyzoites. Bradyzoites are indicative of the chronic stage of infection and can persist for the life of the individual (Elsheikha and Morsy, 2009).

Review and General Discussion

Epidemiology: Congenital toxoplasmosis occurs worldwide. Congenital transmission occurs during acute toxoplasmosis in a sero-

negative mother when tachyzoites present in the blood might cross the placenta and infect the fetus (Jones *et al*, 2009). The prevalence varies geographically according to primary *Toxoplasma* infection in women risk of child-bearing age (McAuley *et al*, 2009). The parasite is mainly acquired during childhood and adolescence. In industrially developed, temperate climate countries, the prevalence of infection declined over the last 30 years [Welton and Ades, 2005), with 10 to 50% of adults aged 15 to 45 years displaying serological evidence of past infection (Gilbert, 2000). Much higher rates of infection (up to 80%) were found in the tropics in communities exposed to contaminated soil, undercooked meat, or unfiltered water (Remington *et al*, 2006). In contrast to Europe and North America, acquisition of toxoplasmosis during childhood or adulthood in Brazil accounts for high levels of eye disease. In parts of Brazil, up to 20% of the population has toxoplasmic retinochoroiditis, resulting in high levels of visual impairment (Portela *et al*, 2004). Toxoplasmosis is a leading cause of blindness in South America (de Boer *et al*, 2003), but not in Europe or North America (de Boer *et al*, 2003).

The highest rates of infection with *T. gondii* were reported in Europe, Central America, Brazil, and Central Africa (Berger *et al*, 2009). The environment plays a key role in perpetuating the life cycle of *T. gondii*, and warm, humid climates are ideal. In parts of Central America, seropositivity starts around one year of age, when children begin playing in contaminated soil, and it reached 50 to 75%, by adolescence. In other areas, transmission occurs primarily through the ingestion of undercooked meat. In these areas, depending on eating customs, seropositivity might begin in adolescence (or sooner) and could continue throughout adulthood. In many parts of the world, the pattern is mixed.

Estimates of the prevalence of congenital toxoplasmosis based upon serologic screening of neonates or infants range from approximately 1 per 1000 live births in some areas of Latin America to 1 per 10,000 live births in the United States (Guerina *et al*, 1994). The incidence of congenital toxoplasmosis in some European countries with high rates of seroprevalence declined between the 1990s and early 2000s, likely owing to aggressive screening recommendations and national prevention programs (Varella *et al*, 2009). Generally, incidence of maternal infection during pregnancy ranged from 1 to 8/1000 susceptible pregnancies, with the highest reported rates in France (Gilbert and Peckham, 2002). The risk of transmitting infection to the fetus increases steeply with the gestational age at seroconversion (Thiébaut *et al*, 2007). Immunocompetent women infected prior to conception virtually never transmit toxoplasmosis to fetus, although rare exceptions have been reported (Voge *et al*, 1996). The immunocompromised women (e.g., women with AIDS or taking immunosuppressive medications) may have parasitemia during pregnancy despite the preconceptional infection; their infants were at risk of congenital infection (Desmonts *et al*, 1990).

In some Arabian and African countries data were scattered. Toxoplasmosis among women ranged from 22.5 to 37.4% in Saudi Arabia (Shoura *et al*, 1973; Abbas *et al*, 1986), 37.5% in Libya (Kassem and Morsy, 1991), 37% in Jordan (Morsy and Michael, 1980), 95.5% in Kuwait (Behbehani and Al-Karmi, 1980), in Egypt, pregnant women 22.2% and non-pregnant ones 20% showed *T. gondii* antibodies (Saleh *et al*, 2014). In Dar es-Salaam (Tanzania) a sero-prevalence of 35% was reported in pregnant women (Doehring *et al*, 1995). In Sudan Elnahas *et al*. (2003) over 65% women were at risk of sero-conversion during pregnancy. In Rabat (Morocco) a recent infection was 93.5% with IgM positive sera (El Mansouri *et al*, 2007).

Congenital toxoplasmosis secondary to reinfection was a rare event; this phenome-

non has been reported in approximately six women over the past three decades. One well-documented case demonstrated that prior immunity to toxoplasma did not protect against reinfection with an atypical strain (Elbez-Rubinstein *et al*, 2009).

Pathogenesis: The oocyst, bradyzoite, and tachyzoite stages of *T. gondii* all can cause disease in humans (Dubey and Jones, 2008). Congenital infection typically occurs via the transmission of tachyzoites through the placenta after a primary maternal infection during pregnancy, but rarely may occur after reactivation of disease in an immunocompromised pregnant woman (Montoya and Remington, 2008). The risk of transmission to the fetus during an acute maternal infection varies depending upon the gestational age during which maternal infection occurs. As the gestational age increases, the risk of infection in the fetus increases, but the severity of the disease decreases (Elsheikha *et al*, 2008).

Without treatment, most fetuses infected early in pregnancy die in utero or in the neonatal period or develop severe neurologic and ophthalmologic sequelae. Those infected in the second and third trimesters typically have mild or subclinical disease at birth. In addition to gestational age at the time of fetal infection, severity of congenital toxoplasmosis also is influenced by host immune responses and the virulence of the *T. gondii* strain (Jamieson *et al*, 2008).

Congenital toxoplasmosis has the broad spectrum of nonspecific clinical manifestations. The so-called classic triad of congenital toxoplasmosis consists of the chorioretinitis, hydrocephalus, and intracranial calcifications. However, the classic triad occurred in less than 10% of cases, and most newborns with congenital toxoplasmosis were asymptomatic (Tamma, 2007). There are four types of clinical presentation (Remington *et al*, 2011): 1- Subclinical infection. 2- Severe disease in the neonatal period, 3- Mild or severe disease in the first few months of life, and 4- Sequelae or relapse (usually ocular) of undiagnosed infection later in infancy, childhood, or adolescence.

Subclinical infection: Most (70 to 90%) newborns with the congenital *Toxoplasma* infection have no manifestations on routine physical examination (Desmonts and Couvreur, 1974). More specific testing, such as examination of cerebrospinal fluid (CSF), detailed ophthalmologic examination, and central nervous system (CNS) imaging may reveal abnormalities and is recommended when there is a high index of suspicion of congenital infection. Among 48 infants with congenital toxoplasmosis diagnosed through a newborn screening program who had normal newborn examinations, 40% had CNS or retinal abnormalities (Couvreur *et al*, 1984). Ophthalmologic lesions often consist of unilateral macular retinal scars. CNS lesions always as small, focal cerebral calcifications; there might be mild to moderate elevations of CSF protein, sometimes >1g/dL, and mononuclear CSF pleocytosis.

Clinically apparent disease: The signs and symptoms of congenital toxoplasmosis are present in only 10 to 30% of infants at birth and symptomatic infection usually results from primary maternal infection during the first trimester (Hampton, 2015).

The clinical findings are multiple and nonspecific; they may be localized to the CNS or eye, or they may be generalized (McAuley *et al*, 1994). In a case series from the 1940s in which 98% of 156 cases had clinically apparent disease, the following data were presented in >50% of cases (Eichenwald, 1959): a- Chorioretinitis (86%), b- Abnormal cerebrospinal fluid (63%), and c- Anemia (57%). Findings present in >25 to 50% of cases included: 1- Jaundice (43%), 2- Seizures (41%), 3- Splenomegaly (41%), 4- Hepatomegaly (41%), 5- Fever (40%), 6- Intracranial calcification (37%0. 8- Lymphadenopathy (31%), and 9- Pneumonitis (27%). The other common findings included vomiting (25%), hydrocephalus (20%), eosinophilia (9%), rash (8%), and abnormal bleeding (7%).

McLeod *et al*. (2006) in Chicago reported that 120 infants with congenital toxoplasmosis with the exception that some findings occurred more frequently: jaundice (about 60%), thrombocytopenia (about 40%), intracranial calcifications (85%), microphthalmia (about 20%), and hydrocephalus (50%).

Late manifestations: Newborns with mild or subclinical congenital *Toxoplasma* disease at birth remain at significant risk for long-term sequelae, particularly if they do not receive extended anti-*Toxoplasma* therapy (Wilson *et al*, 1980).

On the other hand, immunocompetent persons with primary infection are asymptomatic, but latent infection can persist for the life of the host. In immunosuppressed patients, especially patients with the acquired immunodeficiency syndrome (AIDS), the parasite can reactivate and cause disease, usually when the CD4 lymphocyte count falls below 100 cells/mm^3. All the patients with human immunodeficiency virus (HIV) infection should be screened for *T. gondii* antibodies. Counseling on preventing toxoplasmosis should be given to those who are seronegative and prophylaxis initiated, when appropriate, for seropositive patients (Luft and Remington, 1992). Among the HIV-infected patients, seroprevalence of *T. gondii* mirror rates of seropositivity in the general population. In the United States, *T. gondii* seroprevalence was 15% percent and did not differ based upon whether or not the individual had HIV (Falusi *et al*, 2002). Those with HIV were more likely to have antibodies to *T. gondii* if they were ≥50 years of age or born outside of the United States. In patients with AIDS, there was no higher incidence of toxoplasmosis in cat owners compared to the non-cat owners (Wallace *et al*, 1993). Patients with AIDS and <100 CD4 cells/mm^3, who were *Toxoplasma* seropositive, had an approximately 30% probability of developing reactivated toxoplasmosis if they did not receive effective prophylaxis, reactivation site is especially the central nervous system (San-Andrés *et al*, 2003). Ng'walali *et al*. (2001) in Tanzania reported a 35-year old man with fulminant *Toxoplasma* encephalitis in HIV-infected patient.

Chorioretinitis: The commonest late manifestation is chorioretinitis. The incidence of new-onset retinal lesions in untreated children approaches 90%, and the risk extends into adulthood (Phan *et al*, 2008). *Toxoplasma* chorioretinitis, more simply known as ocular toxoplasmosis, is probably the commonest cause of infections in the back of the eye (posterior segment) worldwide, most cases are acquired congenitally (Papadia *et al*, 2011). The toxoplasmic chorioretinitis appears as raised yellow-white, cottony lesions in a non-vascular distribution, unlike the perivascular exudates of CMV retinitis. Vitreal inflammation is usually present in contrast to ocular toxoplasmosis in immunocompetent patients. The chorioretinitis due to *T. gondii* could rarely mimic acute retinal necrosis (Moshfeghi *et al*, 2004). The commonest symptom is the decreased visual acuity in one eye. The diagnosis is made by examination of the eye, using ophthalmoscopy. Sometimes serologic testing is used to rule out the disease, but due to high rates of false positives, serologies are not diagnostic of toxoplasmic retinitis.

The typical lesion is a focal necrotizing retinitis (Mets *et al*, 1997). Associated findings may include microphthalmia, strabismus, cataract, and nystagmus. Complications of *Toxoplasma* chorioretinitis include vision loss, retinal detachment, and neovascularization of the retina and optic nerve. Other sequelae include cataracts, glaucoma, and changes in the iris. The differential diagnosis of chorioretinitis in infants includes other congenital infections associated with retinal lesions (e.g., cytomegalovirus, herpes simplex virus, rubella, varicella, syphilis); congenital anomalies; and congenital hypertrophy of the retinal pigmented epithelium (Hanshaw and Dudgeon, 1978).

Other late manifestations: Other late manifestations of congenital toxoplasmosis include (Sever *et al*, 1988): a- Motor and cere-

bellar dysfunction, b- Microcephaly, c- Seizures, d- Intellectual disability (mental retardation), and e- Sensorineural hearing loss.

Also, Setian *et al.* (2002) added growth retardation and other endocrine abnormalities, such as the precocious puberty (secondary to hypothalamopituitary dysfunction).

Differential diagnosis: Toxoplasmosis infection must be differentiated from other intrauterine infections with similar manifestations in the newborn, and other conditions cause retinal lesions. These include:

1- Rubella (Congenital rubella infection (CRI) encompasses all outcomes associated with intrauterine rubella infection as miscarriage, stillbirth, combinations of birth defects, asymptomatic infection (Reef *et al*, 2000). Congenital rubella syndrome (CRS) refers to variable constellations of birth defects as the hearing impairment, congenital heart defects, cataracts/ congenital glaucoma, pigmentary retinopathy…etc. (Plotkin *et al,* 1996). Newborns with CRS remain actively infected and contagious at the birth time (Cherry, 2009). Droplet precautions should be instituted for hospitalized patients as soon as rubella or congenital rubella infection is suspected (Plotkin *et al,* 2011). Rubella virus is spread from person to person via airborne transmission or droplets shed from respiratory secretions or may be transmitted by persons with subclinical or asymptomatic infection. However, no special precautions are necessary in the household setting for infants with CRS. However, the family should be advised about the potential risks to pregnant visitors and the individuals known to be rubella immune should care for contagious or potentially contagious patients (CDC, 2011).

2- Cytomegalovirus (CMV) is a ubiquitous virus that commonly infects people across the spectrum of all ages, races, and ethnic groups, and those from a variety of socioeconomic, cultural, and geographic backgrounds. Although most CMV infections are asymptomatic or cause mild disease, the virus could cause serious disease in the newborns and immunocompromised children (Demmler-Harrison, 2009). Approximately 1% (0.2 to 2.5%) of newborns was born congenitally infected with CMV (Mocarski, 1996). Most of these newborns appear normal and are asymptomatic, but 5 to 15% of congenitally infected newborns have symptoms at birth. Both maternal primary and recurrent infection during pregnancy can result in congenital infection of the infant, but the rate of transmission is far higher for mothers with primary infection (40 vs. <1% transmission). Infants born congenitally infected with CMV as a result of a primary maternal infection also are much more likely to have symptoms at birth and suffer sequelae (Demmler, 1991). Preventing cytomegalovirus (CMV) infection is difficult because the virus is so ubiquitous and infection occurs so commonly. However, in certain circumstances, trying to prevent CMV infection is desirable (Paya, 2001).

3- Syphilis (Congenital syphilis occurs when the spirochete *Treponema pallidum* is transmitted from a pregnant woman to her fetus. Infection can result in stillbirth, prematurity, or a wide spectrum of clinical manifestations; only severe cases are clinically apparent at birth (CDC, 2010b). Early congenital syphilis is arbitrarily defined by clinical manifestations with onset before two years of age (Dobson *et al*, 2009). Manifestations of early clinical syphilis are varied and unpredictable, about 40 to 60% of the symptomatic infants have at least one of the following: hepatomegaly, nasal discharge ("snuffles"), rash, generalized lymphadenopathy, or skeletal abnormalities (Rawstron and Hawkes, 2012). Late congenital syphilis is related to scarring or persistent inflammation from early infection and are characterized by gumma formation in various tissues (Chakraborty and Luck, 2008). Late congenital syphilis develops in about 40% of infants born to women with untreated syphilis during pregnancy. Some manifestations of the late congenital syphilis can be prevented by treatment of the mother during

pregnancy or treatment of the infant within the first three months of life (Stamos and Rowley, 1994).

However, other manifestations as keratitis, saber shins) might occur or progress despite appropriate therapy (Oksala, 1957). The diagnosis of congenital syphilis should be suspected in all infants born to women who have reactive nontreponemal and treponemal tests for syphilis and infants/children with clinical findings compatible with congenital syphilis (Workowski *et al*, 2010).

4- Congenital lymphocytic choriomeningitis virus syndrome: a disease that mimics the congenital toxoplasmosis or Cytomegalovirus infection. Congenital LCM virus infection could be an under-recognized cause of congenital infection among infants born in the United States. Because of the clinical similarities of these congenital infections, cases of congenital LCM virus infection can be confused with infections with cytomegalovirus or *Toxoplasma gondii* (Wright *et al*, 1997). This disease must be differentiated from Toxoplasmosis, Other (i.e. Syphilis, VZV, EBV, HIV, West Nile Virus), Rubella, Cytomegalovirus (CMV), Herpes Simplex Virus (HSV), Inherited Aicardi Syndrome (lethal in males), Choroideremia and/or Gyrate Atrophy (Lucas *et al*, 2009). CDC (2014) stated that LCMV is most commonly recognized as causing neurological disease, as its name implies, though infection without symptoms or mild febrile illnesses are more common clinical manifestations. The onset of symptoms usually occurs 8-13 days after exposure to virus as part of a biphasic febrile illness. This initial phase, which may last as long as a week, typically begins with any or all of the following symptoms: fever, malaise, lack of appetite, muscle aches, headache, nausea, and vomiting. Other less frequent symptoms include sore throat, cough, joint pain, chest pain, testicular pain, and parotid (salivary gland) pain. Following few days of recovery, a second phase of illness may occur. Symptoms may consist of meningitis (fever, headache, stiff neck, etc.), encephalitis, or meningoencephalitis. LCMV causes acute hydrocephalus (increased fluid on the brain), which often requires surgical shunting to relieve increased intracranial pressure. In rare instances, infection results in myelitis and presents with symptoms such as muscle weakness, paralysis, or changes in body sensation. An association between LCMV infection and myocarditis was suggested.

5- Congenital retinal anomalies: Cogan (1971) clinically classified congenital retinal anomalies under the following headings: a- Coloboma-orbital cyst-"anophthalmos" group due to aberrant closure of the embryonic fissure; b- Retinal fold-central stalk-detachment group comprising a series that varies from simple retinal folds to total retinal detachment and anomalous stalk formation. Cases of the 13-15 trisomy syndrome constitute a special subgroup in this rubric; c- Retrolental fibroplasia, due to hyperoxia of premature infants, is manifest by "dragged" disks and gliovascular proliferation with occasional detachment; d- Persistent hyaloid system is occasionally associated with mild anomalies of the retina; e- Massive gliosis of the retina is usually a hamartomatous manifestation; f- Congenital absence of ganglion cells occurs with cerebral maldevelopment and g- Congenital absence of the photoreceptors is the congenital form of retinitis pigmentosa.

6- Congenital hypertrophy of the retinal pigmented epithelium: Generally, CHRPE displays hypoautoflouorescence and hyporeflectivity with hyper-reflective lacunae on IR imaging. On EDI-OCT, CHRPE seems flat with thickened, irregular RPE and absent RPE within lacunae. A prominent feature is outer retinal loss, generally involving the outer nuclear layer to photo-receptors, occasionally with a characteristic sub-retinal cleft (Fung *et al*, 2014). Serology, the ophthalmologic evaluation, and central nervous system imaging usually can differentiate congenital toxoplasmosis from these conditions.

7- Congenital toxoplasmosis from reactivat-

ion of latent infection in a severely immunodepressed HIV-infected pregnant woman, with poor adherence to therapy was reported (Fernandes et al, 2009).

Evaluation and diagnosis: Timely diagnosis of congenital toxoplasmosis infections facilitates early initiation of therapy. Diagnosis may be suspected based upon maternal serology, newborn screening, or clinical manifestations, but it is confirmed with the reference laboratory tests.

Clinical suspicion: Congenital toxoplasmosis should be suspected in (Carter and Frank, 1986): 1- Infants born to women who have evidence of primary *T. gondii* infection during gestation, 2- Infants born to women who are immunosuppressed and have serologic evidence of past infection with *T. gondii*, and 3- Infants who have compatible clinical findings (e.g., intracranial calcifications, chorioretinitis, otherwise unexplained mononuclear cerebrospinal fluid (CSF) pleocytosis or elevated CSF protein).

Infants who have a positive screening test for *Toxoplasma* IgM, in regions where such serologic screening is a must (Naot *et al*, 1981). The newborn screening is to detect disorders that are threatening to life or long-term health before they become symptomatic. These conditions include inborn errors of metabolism, endocrine disorders, hemoglobinopathies, and perinatally acquired infectious diseases (Kaye, 2008). Early treatment of these rare disorders may significantly reduce mortality and morbidity in affected patients. About four million infants born annually in the United States undergo screening for genetic and metabolic diseases. Newborn screening is the universally accepted public health program that integrates sample collection, laboratory testing, follow-up, diagnosis, treatment of identified disease, and tracking of outcomes (Pass *et al*, 2000). Given the potential difficulty in interpreting serologic tests in newborn infants, all infants with possible congenital toxoplasmosis must undergo the additional clinical, laboratory, and imaging evaluation for evidence of congenital toxoplasmosis.

Clinical evaluation: The evaluation of the newborn with suspected congenital toxoplasmosis should include a review of maternal history and serology (if available), complete physical examination, *T. gondii* serology, and evaluation for the ophthalmologic, neurologic, and other manifestations that might not be detected on physical examination (Tab. 1). Dependable diagnosis generally relies upon a combination of clinical and laboratory findings.

The clinical evaluation should include: 1- Eye examination: Chorioretinitis may be the only clinical manifestation. In a cohort of 48 infants with congenital toxoplasmosis who were identified through neonatal serologic screening and who had normal physical examinations, approximately 20% suffered from retinal lesions or scars at birth. The examination should be performed by an ophthalmologist experienced in retinal examinations in newborn and young infants; typically infants are referred to a pediatric ophthalmology clinic (Uhumwangho and Jalali, 2014). 2- Neurologic evaluation, including lumbar puncture and cranial imaging: Central nervous system (CNS) abnormalities may be the only manifestation of congenital toxoplasmosis. In a cohort of 48 infants with congenital toxoplasmosis who were identified through neonatal serologic screening and who had normal physical examinations, 30% had evidence of CNS involvement CNS involvement may manifest with elevated CSF protein (sometimes >1g/dL) or mononuclear CSF pleocytosis. In addition, the detection of *Toxoplasma*-specific IgM in the CSF or isolation of *T. gondii* from the CSF may confirm the diagnosis (Wallon *et al*, 1988). 3- Cranial imaging is performed to assess focal brain lesions or hydrocephalus. They preferred computed tomo-graphy (CT) without contrast as the preferred imaging study because it is fast and less costly than magnetic resonance imaging (MRI), and usually can be done without sedation, and they have found it to be more sensitive than

ultrasonography in detecting the small calcified lesions.

Abnormalities on neuroimaging may include (Friedman *et al*, 1999): 1- Intracranial calcifications, single or multiple, scattered throughout the brain, 2- Hydrocephalus (characteristically secondary to periaqueductal involvement), and 3- Cortical atrophy.

Hearing evaluation: All the newborns with suspected congenital toxoplasmosis should undergo hearing evaluation. Early identification of hearing impairment facilitates early intervention and improved outcomes. *Toxoplasma gondii* was associated with disorders of the auditory pathways since the 1950's (Wright, 1971), when calcium deposits (similar to those found in the brains of children with congenital toxoplasmosis) were found in the spiral ligament and the cochlea (Kelemen, 1958). Congenital toxoplasmosis caused sensorineural deficit in up to 20% of the Brazilian patients and the proper treatment in the first year improved prognosis (Andrade *et al*, 2008).

Laboratory evaluation: The laboratory evaluation for children with suspected congenital toxoplasmosis includes serology, PCR, and other tests that help to confirm infection, evaluate the extent of infection, and to obtain baseline values before initiating antimicrobial therapy. Isolation of *T. gondii* from clinical specimens may also be performed, but this technique requires additional time and is only available in select reference laboratories.

Serology: The diagnosis of congenital toxoplasmosis infection in the newborn usually is made serologically, but the interpretation of serologic results can be complicated, and consultation with an infectious disease specialist may be warranted.

Issues that complicate interpretation of serologic results in the newborn include (Roc *et al*, 2010): 1- Anti-*Toxoplasma* IgG in the newborn reflected past or current infection in the mother (since IgG crosses placenta), 2- Fetal IgM antibody might disappear before birth, 3- Prenatal treatment may affect the serologic profile of the infant; IgM was rarely present in infants who received anti- *Toxoplasma* therapy with Pyrimethamine and Sulfadiazine in utero. Data regarding the effects of prenatal treatment on other antibodies are lacking, 4- The newborn antibody response to *T. gondii* might be delayed for months, and 5- Placental leakage of maternal IgM or IgA might result in low positive IgM or IgA in an uninfected infant shortly after birth.

For an accurate serologic diagnosis, testing of blood samples from both the infant and his mother is required. Immunologically normal women with acute *Toxoplasma* infection in pregnancy typically have positive *Toxoplasma* IgG & IgM antibodies (Villard *et al*, 2013).

Diagnosis in the newborn relies on the presence of *Toxoplasma*-specific IgM by ELISA or by immunosorbent agglutination assay (ISAGA). *Toxoplasma*-specific IgM may be demonstrated within the first few days of life or may appear at variable times after birth (depending upon the timing of maternal infection). Thus, negative *Toxoplasma*-specific IgM did not exclude the congenital infection (Torgerson and Mastroiacovo, 2013)

When the infant's IgM titers are negative or equivocal, IgA and IgE ELISA should be performed (Wong *et al*, 1993), Detection of *Toxoplasma*-specific IgA or IgE was more sensitive than detection of IgM for congenital toxoplasmosis (approximately 90 vs. 75 to 80%), but the specificity was not assured (Decoster *et al*, 1988). None of the currently available commercial assays offered in the United States were cleared by the FDA for in vitro diagnostic use for infants, and confirmation in a reference laboratory as the Toxoplasmosis Serology Laboratory at the Palo Alto Medical Foundation was suggested (CDC, 2010a). Outside the United States, there are a number of countries with reference or special interest laboratories that perform maternal and newborn serology for *T. gondii*. Specific examples of reference la-

boratories include the World Health Organization/Food and Agriculture Organization of the United Nations (WHO/FAO) International Centre for Research and Reference on Toxoplasmosis (Staten Serum Institute, Copenhagen, Denmark) and the *Toxoplasma* Reference Laboratory, Public Health Laboratory (Singleton Hospital, Swansea, United Kingdom), and others (Petersen *et al,* 2005).

Repeat testing at 10 days of age can help to make the diagnosis. IgM and IgA titers in an infant who is not infected (ie, in an infant with low positive IgM and IgA titers as a result of placental leak) will decrease rapidly, whereas the titers will remain positive for weeks to months in an infant who was infected in utero (Stepick-Biek *et al,* 1990).

Serial serologic testing during the first year of life is required for diagnosis when the initial results are equivocal. Transplacentally derived the maternal *Toxoplasma*-IgG titers usually fall to undetectable levels between 6 and 12 months of age. In contrast, infants with congenital infection typically have elevated *Toxoplasma*-specific IgG levels beyond one year of age (McAuley, 2008). Decisions regarding treatment in equivocal cases must weigh the risks and benefits of initiating treatment without a definitive diagnosis versus waiting for confirmation of the diagnosis (which may take months).

Demonstration of *T. gondii*: Isolation or histologic demonstration of *T. gondii* or the *T. gondii* nucleic acids from clinical specimens in conjunction with compatible clinical and/or serologic findings can confirm the diagnosis of congenital toxoplasmosis. These methods are used less frequently than serology because they are not widely available and may require tissue specimens (Rifaat *et al,* 1977).

Laboratory methods that involve isolation or demonstration of *T. gondii* include (Filisetti *et al,* 2010): 1- Positive *T. gondii* polymerase chain reaction (PCR). The PCR on amniotic fluid is particularly useful for the diagnosis of fetal infection. PCR can also be used on brain tissue, cerebrospinal fluid, vitreous fluid (ocular *Toxoplasma*), urine, peripheral blood, and broncho-alveolar lavage fluid, cord blood, newborn peripheral blood, cerebrospinal fluid, or placenta. 2- Observation of parasites (e.g., demonstration of cysts) in body fluids or tissues (e.g., placenta). 3- Isolation of parasites from blood orbody fluids by mouse inoculation or tissue culture; these require two to six weeks for completion (Boyer, 2001).

Other laboratory tests: Other laboratory tests that should be included in the initial evaluation of the infant with suspected congenital toxoplasmosis include (Tab. 1): 1- Lumbar puncture to obtain CSF for protein, glucose, cell count, and *T. gondii* PCR. The *Toxoplasma*-specific IgG & IgM in CSF also may be useful. CSF PCR and serologies are performed in reference laboratories. 2- Complete blood count with differential and platelet count (anemia, thrombocytopenia, and eosinophilia are common nonspecific manifestations in symptomatic infants). 3- Liver function tests (aspartate aminotransferase, alanine aminotransferase, total and direct bilirubin). 4- Serum creatinine and urinalysis (before initiating treatment with sulfadiazine, sulfamerazine, or sulfamethazine); the dosing of these agents requires adjustment in patients with renal insufficiency.

Evaluation for glucose-6-phosphatase dehydrogenase deficiency must be done before treatment with sulfadiazine, sulfamerazine, or sulfamethazine. Celik *et al.* (2013) reported that testing for G6PD must be ordered to all newborns who are receiving phototherapy and especially to those who are coming from the high incident geographical regions and less responsive to phototherapy. Molad *et al.* (2013) reported that in severe cases with persistent anemia one should search after delivery for a second reason other than G6PD deficiency alone. Besides, Soliman *et al.* (1985) reported toxic effect of pyrimathamine® in experimental animals

The quantitative serum immunoglobulins (IgG, IgM, & IgA) may be useful in the confirmation of congenital infection. The ratio

of *Toxoplasma*-specific IgG to total IgG decreases in the second to third month in infants without congenital toxoplasmosis and remains stable or increases in infants with congenital toxoplasmosis (Gontijo da Silva *et al*, 2015). Oliveira *et al.* (2015) reported that *T. gondii*-specific IgG, IgM and IgA antibodies in serum and colostrum samples from puerperal women may be detected with a significant correlation, suggesting that colostrum may also be used as an alternative biological sample to efficiently diagnose recent human toxoplasmosis.

Urine culture for cytomegalovirus might have similar clinical manifestations, and/or occur as a concomitant infection (Wright *et al*, 1997). The clinical presentation in some symptomatic toxoplasmosis infants could overlap with many other congenital infections (e.g., rubella, syphilis, congenital lymphocytic choriomeningitis virus syndrome, and congenital retinal anomalies), but these usually can be distinguished from congenital toxoplasmosis through serology (mother and infant), maternal prenatal and postnatal history and routine screening tests, ophthalmologic evaluation, and central nervous system imaging.

Interpretation: Among infants not diagnosed prenatally, congenital toxoplasmosis was confirmed or highly likely in the following scenarios (Contopoulos-Ioannidis and Montoya, 2012). *Toxoplasma*-specific IgM, IgA, or IgE in the serum of newborns with compatible maternal serology; contamination with maternal blood should also be reasonably excluded (Rabilloud *et al*, 2010).

Characteristic clinical findings (chorioretinitis, intracranial calcifications, and/or hydrocephalus) in the infant born to a mother with documented primary infection during pregnancy (or chronic *Toxoplasma* infection if the mother is *immune* compromised). Contributing laboratory findings in this setting would include abnormal CSF profile or positive *Toxoplasma* PCR (Gilbert *et al*, 2007).

Serial serology is a must to confirm or exclude congenital toxoplasmosis in infants who have positive initial serology in the absence of clinical abnormalities. In such cases, decisions regarding treatment must weigh the risks and benefits of initiating the treatment without a definitive diagnosis versus waiting for confirmation of the diagnosis (which may take months).

Congenital toxoplasmosis is confirmed if there was (Dard *et al*, 2017): 1-An increase in anti-*Toxoplasma* IgG titer during the first year of life or increasing IgG titer compared with the mother's; the congenitally infected infant usually can synthesize *Toxoplasma* IgG by the third month of life if he or she is not treated; synthesis may be delayed until six to nine months of age in treated infants, and 2- Persistence of anti-*Toxoplasma* IgG at one year of age (by which time transplacentally acquired maternal IgG should have disappeared).

In the absence of treatment, congenital toxoplasmosis is excluded if serial serologic testing showed a continuous decline in IgG titer in the absence of *Toxoplasma*-specific IgM or IgA, provided that the child is capable of synthesizing IgG (assessed by measurement of serum quantitative immunoglobulins). Titers may decline with IgM becoming negative while on treatment; these infants typically have a rebound rise in IgM when retested one to several months off of treatment (Sarwat *et al*, 1993).

Treatment or Antiparasitic therapy: Treatment with antiparasitic therapy for infants (<12 months) in whom a diagnosis of congenital toxoplasmosis is confirmed or highly likely, including (McAuley *et al*, 1994): 1- Infants diagnosed with congenital toxoplasmosis prenatally (whether or not their mothers received chemotherapy). 2- Infants with suspected congenital toxoplasmosis who have confirmation serology or PCR performed by a reference laboratory. 3- Infants with evidence of recent maternal *T. gondii* infection in conjunction with the clinical findings compatible with congenital toxoplasmosis in the infant (chorioretinitis, intracranial calcifications, and /or hydrocephalus)

Given the increased risk of late sequelae in untreated congenital toxoplasmosis, we also suggest antiparasitic treatment for asymptomatic infants with equivocal newborn serology, pending definitive diagnosis, which may take months (Remington *et al*, 2011).

Treatment regimen: The preferred antiparasitic regimen includes pyrimethamine and sulfadiazine (or sulfamerazine or sulfamethazine) and folinic acid (McAuley *et al*, 2009). Sulfamerazine and sulfamethazine are not available in the United States. The optimal doses and duration for these drugs are not established definitively and should be determined in consultation with specialists in pediatric infectious diseases.

Pyrimethamine 2mg/kg (maximum 50mg/dose) once daily for two days; then 1mg/kg (maximum 25mg/dose) once daily for six months; and then 1mg/kg (maximum 25mg/dose) every other day (i.e., Monday, Wednesday, and Friday) to complete one year of therapy, and Sulfadiazine 100mg/kg/day divided in two doses every day for one year, plus Folinic acid (leucovorin) 10mg three times per week during and for one week after pyrimethamine therapy.

For infants with clinical evidence of toxoplasmosis, combination therapy for one year was associated with decreased incidence of long-term complications and decreased incidence of new-onset ocular disease compared with no treatment or treatment for shorter periods (Roizen *et al*, 1995). Treatment for one year was recommended (ContopoulosIoannidis and Montoya, 2012). However, in some centers, treatment is continued for two years.

Glucocorticoids (prednisone 0.5mg twice/day) were added if cerebrospinal fluid (CSF) protein is >1 g/dL or when active chorioretinitis threatens vision. Glucocorticoids are continued until resolution of elevated CSF protein or active chorioretinitis that threatens vision. The benefit of adjunctive glucocorticoids has not been demonstrated in controlled trials; adverse effects have not been noted in cohort studies. The infant should be weighed weekly and the doses adjusted accordingly. Pyrimethamine should be temporarily withheld if the absolute neutrophil count (ANC) falls below 500cells/microL. Dose of folinic acid must be increased as needed if ANC was below 1000cells/microL

For infants who develop an allergy to sulfadiazine, clindamycin (20 to 30mg/kg/day divided into four doses) may be substituted (Dannemann *et al*, 1992). Skin exanthems (hives, allergic dermatitis) are the commonest allergic reactions to sulfadiazine, but severe leucopenia rarely can occur; sulfadiazine-induced leucopenia should be considered in any infant who develops leucopenia unresponsive to increased folinic acid dosing or temporary discontinuation of pyrimethamine.

Special considerations are necessary for the children with renal insufficiency or glucose-6-phosphate-dehydrogenase (G6PD) deficiency and those taking anticonvulsant or antiretroviral therapy (Katlama *et al*, 1996).

Sulfadiazine is excreted in the kidney, and the dose may require adjustment for infants with renal insufficiency. Sulfadiazine may cause hemolysis in children with G6PD deficiency; clindamycin may be substituted for sulfadiazine in children with G6PD deficiency. The combination of pyrimethamine and clindamycin has been used to successfully treat toxoplasmic encephalitis in patients with AIDS (Dannemann *et al*, 1988) and the authors have used it without complications in a child with severe G6PD deficiency. They recommended the use of pyrimethamine and clindamycin in several children who developed sulfadiazine allergy. However, high-dose pyrimethamine was reported to cause hemolytic anemia in some patients with G6PD deficiency, and such patients should be monitored closely. Combination antiparasitic therapy is recommended for treating *Toxoplasma* infection, so in children not able to take either pyrimethamine or sulfadiazine, clindamycin plus an alternative agent should be selected in consultation with an infectious disease expert.

Sulfadiazine prolonged phenytoin half-life of by interference with hepatic microsomal enzymes, and dose adjustment (Gilbert and Dezateux, 2006).

As to toxoplasmosis and HIV, the commonest extracerebral sites in HIV-infected patients were the heart, lungs, and pancreas with 91, 61, & 26% of cases, respectively also, the spinal cord and CNS (Hofman *et al*, 1993). During acute toxoplasmosis, symptoms are often influenza-like: swollen lymph nodes, or muscle aches and pains for a month or more. Rarely, a patient with a fully functioning immunesystem may develop eye damage. Young children and immunocompromised patients, with HIV/AIDS, those on certain types of chemotherapy, or those who have recently received an organ transplant, may develop severe toxoplasmosis. This could cause damage to brain or eyes (Paquet *et al*, 2013).

First-line therapies for cerebral toxoplasmosis and HIV/ADIS include pyrimethamine plus sulfadiazine or pyrimethamine and clindamycin: Pyrimethamine (200mg loading dose followed by 50mg PO daily in patients <60kg or 75mg daily in patients >60kg) and Sulfadiazine (1000mg four times PO daily in patients <60 kg to 1500mg four times PO daily among patients >60 kg) and Leucovorin 10 to 25mg PO daily (Rabaud *et al*, 1994). Alternatives are trimethoprim-sulfamethoxazole, pyrimethamine and azithromycin, pyrimethamine and atovaquone, or sulfadiazine and atovaquone (Katlama *et al*, 1996). The folinic acid must always accompany the pyrimethamine therapy (Jordan *et al*, 2004). The doses of pyrimethamine /sulfadiazine or the pyrimethamine/ clindamycin were usually lowered for maintenance of treatment after approximately six weeks of therapy. Corticosteroids were given in conjunction with antibiotics in patients with signs of significant increased intracranial pressure (Béraud *et al,* 2009).

Conclusion

Congenital toxoplasmosis is caused by *T. gondii*, an intracellular protozoan parasite. Congenital toxoplasmosis occurs throughout the world. The prevalence ranged from 1/1000 live births to 1/10,000 live births, depending upon the risk of primary *Toxoplasma* infection in women of child-bearing age.

The transmission toxoplasmosis risk to the fetus during an acute maternal infection increases with increasing gestational age of the fetus, but the infection severity decreases with increasing gestational age.

Most newborns with congenital toxoplasmosis are asymptomatic. But, among symptomatic ones symptoms are nonspecific and may include chorioretinitis, intracranial calcifications, seizures, jaundice, hepatosplenomegaly, lymphadenopathy, anemia, thrombocytopenia, and abnormal cerebrospinal fluid. Late manifestations of untreated congenital toxoplasmosis includes chorioretinitis and neurologic abnormalities (motor abnormalities, intellectual disability, and/or hearing loss), or without any clinical symptoms or findings at birth.

Recommendations

The congenital toxoplasmosis prevention is most often based on the results of a serological screening program in pregnant women followed by prenatal and postnatal treatment of women and their newborns if infection was already established during the pregnancy or ton cord blood (secondary prevention). The primary prevention must not only be based on education about preventive measures given by physicians, but also these guidelines must be reiterated during antenatal classes and leaflets distributed containing the written recommendations on the risk nature of the disease and its avoidance.

1- Differential diagnosis of the congenital toxoplasmosis includes other intrauterine infections and retinal lesions. Timely; congenital toxoplasmosis diagnosis facilitates early initiation of therapy. Diagnosis may be suspected based upon maternal serology, newborn screening, or clinical manifestations, but confirmed with laboratory tests, usually in a reference laboratory.

2- Evaluation of newborn with suspected congenital infection should include a complete physical examination, *T. gondii* serology, and evaluation for ophthalmologic, neurologic, and other manifestations that may not be detected on the physical examination.

3- Diagnosis of congenital toxoplasmosis usually serologically; serial serology may be necessary to confirm or to exclude diagnosis in infants without clinical manifestations.

4- Complete blood counts monitored during therapy are a must to evaluate the drug-induced neutropenia, and hemolysis especially for patients with the G6PD deficiency, the renal insufficiency.

5- Clinical monitoring for the late ophthalmologic and neurodevelopmental manifestations of congenital toxoplasmosis via early childhood.

6- Treated infants remain at risk for long-term sequelae, especially the new-onset ocular disease; recurrence of ocular disease may occur after cessation of treatment. The long-term neurologic deficits usually correlate with the severity of brain injury before the initiation of treatment.

7- Risk factors for poor outcome include delay in the correct diagnosis and thus initiation of treatment, prolonged uncorrected hydrocephalus, cerebrospinal fluid protein >1g /dL, cerebral atrophy, and extensive visual impairment.

8- Health system should offer education that help prevention of toxoplasmosis in females and immunosuppressed patients.

9- Management the livestock and their meat and milk products influence the human toxoplasmosis risk.

10- Health education about toxoplasmosis and its complications should be tailored to women of childbearing age may help to prevent the infection and its complications

Table 1 Initial clinical evaluation of the newborn/infant with suspected congenital toxoplasmosis

Test	Comment
Clinical evaluations	
Complete physical examination	Fever, jaundice, hepatosplenomegaly, and lymphadenopathy common in symptomatic infants (but t examination is normal in most cases)
Ophthalmologist retinal examinations in newborn and young infants	Chorioretinitis only manifestation
Neurologic CT of head without contrast	Intracranial calcifications or hydrocephalus only manifestation
Hearing assessment	Currently recommended for all infants (in the United States)
Lumbar puncture	
CSF glucose, protein, cell count	CSF abnormalities only manifestation; CSF protein may be >1 g/dL in severely affected infants but typically lower in mild or subclinical disease
Toxoplasma-specific PCR*	Can establish diagnosis
Primary serology*˙	
Toxoplasma-specific IgG (ELISA)	Not differentiate maternal from infant infection in newborn period
Toxoplasma-specific IgM (double sandwich ELISA)	Indicative of congenital infection if not contaminated with maternal blood; negative IgM not exclude congenital toxoplasmosis
Additional serology*˙(complementary and more sensitive than primary serology)	
Toxo-specific IgA (ELISA/ISAGA)	Indicative of congenital infection if not contaminated with maternal blood; especially useful if IgG & IgM assays are indeterminate
Toxo-specific IgE (ELISA/ISAGA)	Indicative of congenital infection if not contaminated with maternal blood; especially useful if IgG & IgM assays indeterminate
Blood tests (primarily performed before initiating treatment in confirmed or suspected cases)	
CBC with differential and platelet count	Anemia and thrombocytopenia common in symptomatic infants; also necessary to establish baseline before treatment may cause bone marrow suppression
Evaluation for G6PD deficiency (before initiation of treatment)	Treatment with sulfadiazine may cause hemolysis in G6PD-deficient children
Liver function tests (AST, ALT, total & direct bilirubin)	Primarily for baseline studies before initiating treatment; both direct and cholestatic jaundice may occur in infected infants
Serum creatinine & urinalysis (before initiation treatment)	Sulfadiazine (or sulfamerazine or sulfamethazine) dosing requires adjustment in patients with renal insufficiency
Miscellaneous	
Urine for cytomegalovirus	To exclude congenital cytomegalovirus of similar clinical manifestations; coinfection with cytomeg-alovirus and toxoplasmosis may occur

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