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A Review Article in:

The relationship between Toxoplasmosis and Autism

Submitted to the Council of the College of Medicine, Diyala University, In Partial Fulfillment of Requirements for the Bachelor Degree in medicine and general surgery.

Submitted by:

Asmaa Ismail Sameen

Supervised by:

Asst. Prof. Dr. Rawaa Abdulkhaleq Hussein

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Introduction

Toxoplasma gondii is one of the most frequent human zoonoses, infecting around a third of the world's population. Toxoplasmosis is frequently noticed immunocompetent people; nevertheless, nonspecific flu-like symptoms, lymphadenopathy, and a few unusual complications may be connected to initial infection. Immunocompromised persons and congenitally infected foetuses are also at danger of infection, which can be deadly. The parasite can cross the placenta and infect the foetus, causing retinochoroiditis, hydrocephaly, mental retardation, convulsions, and even foetal mortality in pregnant women (1). The severity of symptoms and risk of congenital infection are determined by the gestational age at which the pregnant woman catches the sickness; the earlier the infection develops during pregnancy, the lower the risk of congenital infection, but the more severe the symptoms. To avoid difficulties, maternal and congenital toxoplasmosis must be diagnosed and treated as soon as feasible. Furthermore, the majority of infected neonates are asymptomatic at birth but suffer vision problems later (2). *T. gondii* can be found in practically every warm-blooded species on the planet. Infection with *Toxoplasma gondii* is common in many parts of the world, with rates as high as 75% reported. There is no substantial difference between males and females in terms of prevalence as they get older. Furthermore, the infection is more prevalent in hot, humid settings (3).

In the first three months of life, premature infants with toxoplasmosis may develop CNS and ocular disease. Full-term infants infected with *T. gondii*, on the other hand, tend to have milder illness, with hepatosplenomegaly and lymphadenopathy in the first two months of life. Despite the fact that most infants infected in utero show no signs

of toxoplasmosis on routine newborn examinations, up to 80% of them develop learning or vision disabilities later in life (4).

There is evidence that infections during pregnancy, especially in the early stages, are associated with neurodevelopmental disorders. Accumulating evidence suggest that toxoplasmosis play a role in triggering and development of many psychiatric and neurological disorders. Autism disorder represents one of the most common neurodevelopmental disorders worldwide. The relationship between prenatal toxoplasmosis and autism in childhood remains unclear and therefore it became a focus of interest for the scientists (5).

Autism is classified as a "spectrum disorder," which means that a child's symptoms can range from moderate to severe. A youngster with autism may find it difficult to communicate and engage with others.It can also lead to a child engaging in repetitive activities and motions, becoming enraged when their daily routine is broken, and having abnormal reactions to particular situations in some cases (6).

Kanner used the word "autism" in 1943 to describe children who couldn't relate to others, had delayed and disordered language, repetitive activities, and a need to fit in (7). Within the first two years of life, autistic disorder symptoms and developmental markers arise. Prior to their child's first birthday, parents have reported developmental concerns, but by the age of two, the majority of parents are concerned about language development and social relatedness. Early developmental impairments include a lack of anticipatory posture, such as reaching out to be picked up, as well as absent or decreased visual cues, smiling in response to others, vocalization, and object exploration. Regression and loss of communication and social abilities are also reported in 20–40% of instances (8).

Review of literature

Toxoplasma gondii was first discovered in the North African mouse Ctenodactylus gundi in 1908 by Nicolle and Manceaux, and was later identified as a cause of human disease in an 11-month-old congenitally infected kid by Nicolle and Manceaux. Janku was born in the year 1923. Wolf, Cowen, and Paige found it in a baby with seizures, cerebral calcifications, hydrocephalus, and chorioretinitis in 1939 and reported it as a cause of encephalitis (9).

Toxoplasma gondii is a parasitic coccidian parasite that lives in cats and warm-blooded animals as intermediate hosts. It is one of the most common animal parasites. It belongs to Phylum Apicomplexa, Class Sporozoasida, Subclass Coccidiasina, Order Eimeriorina, and Family Toxoplasmatidae. There is only one species of Toxoplasma, *T. gondii*. Coccidia in general have complicated life cycles. Most coccidia are host-specific and are transmitted via a fecal–oral route (10).

Parasite morphology

Infective stages

There are three infectious stages of *T. gondii*: the tachyzoites (in groups or clones), the bradyzoites (in tissue cysts), and the sporozoites (in oocysts). These stages are linked in a complex life cycle**.** The tachyzoite is often crescent shaped, approximately 2 by 6 μm, with a pointed anterior (conoidal) end and a rounded posterior end. Ultrastructurally, the tachyzoite consists of various organelles and inclusion bodies including a pellicle (outer covering), apical rings, polar rings, conoid, rhoptries, micronemes, micropore, mitochondrion, subpellicular microtubules, endoplasmic reticulum, Golgi complex, ribosomes, rough and smooth endoplasmic reticula, micropore, nucleus, dense granules, amylopectin

granules (which may be absent), and a multiple-membrane-bound plastid-like organelle which has also been called a Golgi adjunct or apicoplast. The nucleus is usually situated toward the central area of the cell and contains clumps of chromatin and a centrally-located nucleolus (11). As shown in figure (1).

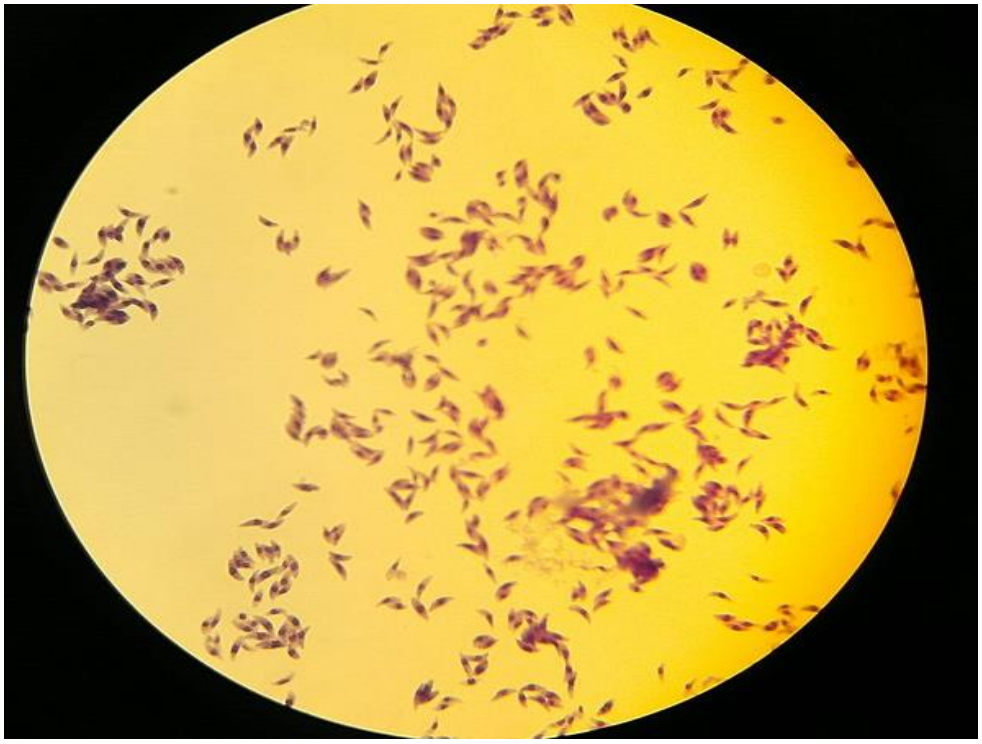

Figure 1. Tachyzoites (12)

Tachyzoites can move by gliding, bending, undulating, and spinning, although they lack apparent locomotion mechanisms like as cilia, flagella, and pseudopodia. The roles of the conoid, rhoptries, micropores, and micronemes are unknown, although they are likely related to parasite penetration and the production of an intracellular environment that is conducive to parasite growth and development (13). Tachyzoites cause immunological responses that result in clinical symptoms in both original and reactivated infection; the presence of tachyzoites is a sign of ongoing infection that requires treatment. They live and multiply in the vacuoles of their hosts' cells, may infect

practically all phagocytic and nonphagocytic cell types, and create rosettes every 6 to 8 hours as shown in figure 3. Continuous multiplication causes cell breakdown and the release of organisms, which either infect surrounding cells or travel to other parts of the body via blood and lymph (14). After a few divisions, *T. gondii* forms tissue cysts that vary in size from 5 to 70 mm and remain intracellular. The tissue cyst wall is elastic and thin (0.5 mm), and it can contain hundreds of *T. gondii* bradyzoites, which are crescent-shaped and slender *T. gondii* stages. The bradyzoites are about 1.5 mm in diameter and differ structurally from tachyzoites just slightly. As shown in in figure (2). They have a nucleus that is placed at the back end, whereas tachyzoites have a nucleus that is more centrally located. Bradyzoites are thinner and less sensitive to proteolytic enzyme degradation than tachyzoites. Although bradyzoites can occur in visceral organs such as the lungs, liver, and kidneys, they are more common in muscular and neural tissues such as the brain, eye, skeletal, and cardiac muscle. Intact tissue cysts are unlikely to cause harm and can live for the rest of the host's life (11).

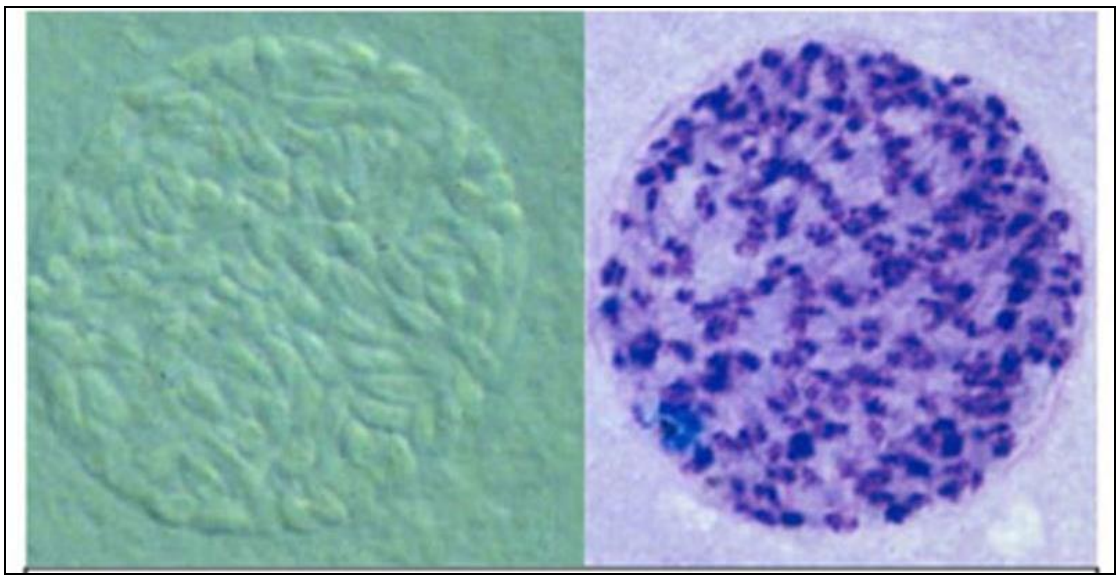

Figure 2. Bradyzoites (15)

Sporozoites grow over several days inside the oocysts that felids shed into the environment as shown in figure (3). Sporozoites excyst and penetrate the distal small intestine of an intermediate host after being eaten. Sporozoites transform into tachyzoites shortly after the initial invasion, and then spread throughout the host. The actual mechanism of sporozoite invasion of host cells has not been investigated, although it is thought to be a two-step process in which the parasite first creates a distended, main vacuole from which it proceeds to create a tighter, secondary vacuole in which it grows. There has been no investigation or identification of the machinery employed in these various processes (16).

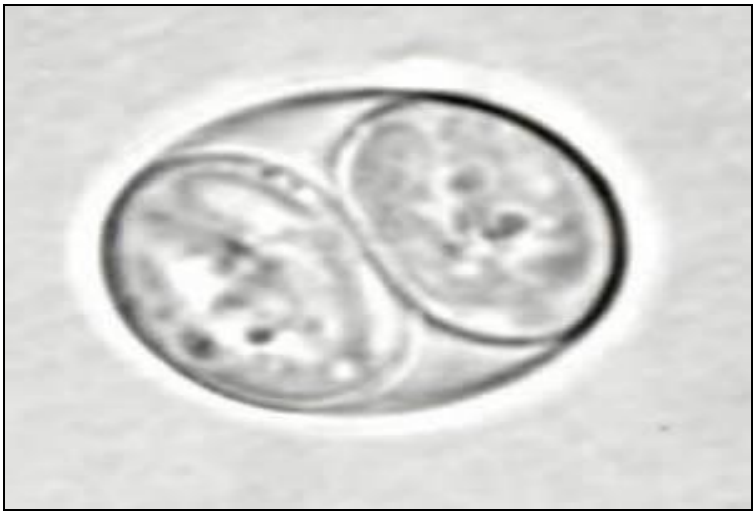

Figure 3. Sporocysts contain sporozoites (17).

Life cycle and transmission

The only definitive hosts for *T. gondii* are members of family *Felidae* (domestic cats and their relatives). In the feces of cats, unsporulated oocysts are shed. Despite the fact that oocysts are only shed for 1–3 weeks on average, enormous numbers can be shed. Oocysts sporulate in the environment for 1–5 days before becoming infective. In nature, intermediate hosts (such as birds and rodents) become infected by

consuming oocyst-contaminated soil, water, or plant material. Shortly after consumption, oocysts turn into tachyzoites. These tachyzoites evolve into tissue cyst bradyzoites in neural and muscular tissue. After consuming intermediary hosts with tissue cysts, cats become sick. Ingestion of sporulated oocysts can also cause infection in cats as shown in figure (4). Tissue cysts can infect animals reared for human consumption and wild wildlife after consuming sporulated oocysts in the environment (18). Humans can become infected by any of several routes (18):

- Eating undercooked meat of animals harboring tissue cysts.
- Consumption of cat feces-infected food or water, as well as polluted environmental samples (such as fecal-contaminated soil or changing the litter box of a pet cat).
- Blood transfusion or organ transplantation.
- Transplacentally from mother to fetus.

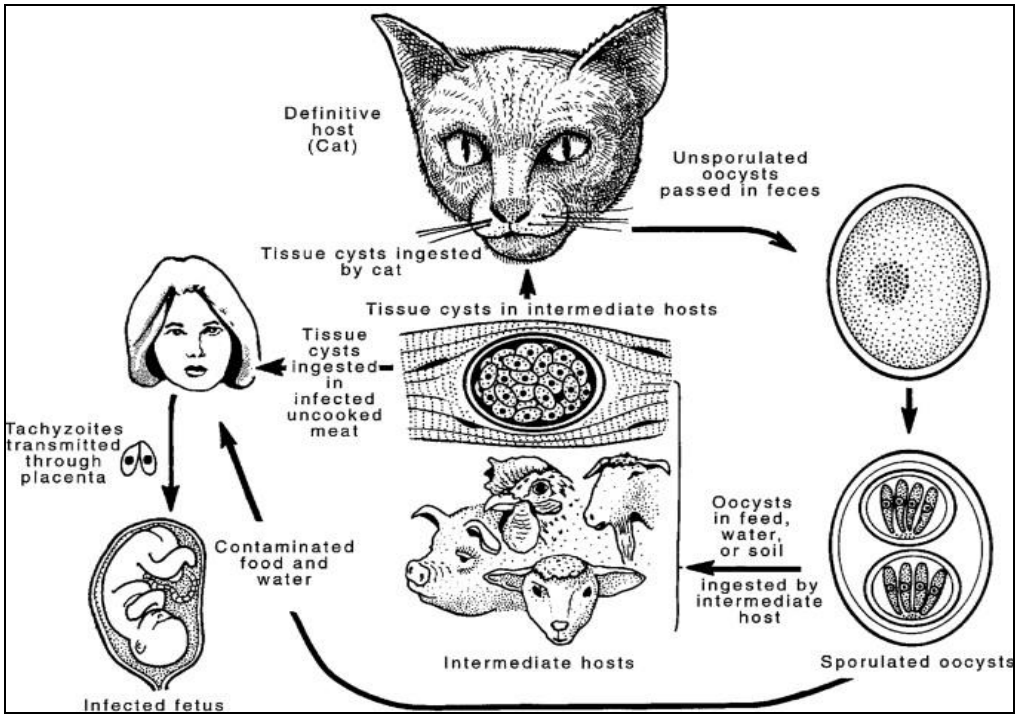

Figure 4. Life cycle of *Toxoplasma gondii* (19).

Pathogenesis

The infection with *T. gondii* is separated into two stages: acute and chronic. Acute infection occurs soon after initial exposure and is characterized by rapid tachyzoite development, tissue damage, and parasite dispersion throughout the host's body. The occurrence of acute infection is linked to clinical symptoms. After the development of human immunity, the tachyzoites stage transforms into bradyzoites, and tissue cysts form, initiating the chronic infection. Tissue cysts can appear as early as 3 days after infection, grow in number until 7 weeks following infection, and last for the rest of the host's life (20). When host immunity is established at the conclusion of the acute phase and the beginning of the chronic phase, tachyzoites undergo stage conversion into bradyzoites and grow slowly to generate tissue cysts with many bradyzoites. When the host's immunity is weakened, the bradyzoites in the cysts can live for the rest of the host's life and can be reactivated to stage convert to tachyzoites (20).

During acute toxoplasmosis, tissue necrosis can occur in the gut, liver, spleen, pancreas, lung, and heart (21). *T. gondii* has the ability to replicate in almost every cell in the body. The exact mechanism by which *T. gondii* is killed in immune cells is unknown. Antibodies impact all external forms of the parasite, but not the intracellular forms. Cellular factors, like as lymphocytes and lymphokines, are thought to be more significant than humoral components in immune-mediated *T. gondii* elimination. Infection is not eradicated by immunity. *T. gondii* tissue cysts can last for years after an acute infection with the parasite. Rupture of a tissue cyst may result in the change of bradyzoites into tachyzoites and renewed proliferation in immunosuppressed individuals, such as those given massive doses of immunosuppressive drugs in preparation for

organ transplants and those with AIDS (22). *T. gondii* pathogenicity is determined by the strain's virulence and the susceptibility of the host species. The pathogenicity of *T. gondii* strains varies depending on the host. Certain mouse strains are more vulnerable than others, and the degree of infection varies even among mice of the same strain. Clinical toxoplasmosis is genetically resistant in several species. Adult rats, for example, do not get sick, but young rats can die from toxoplasmosis (23).

The association with autistic spectrum disorder (ASD)

There is a strong association between toxoplasmosis and mental illnesses like depression, schizophrenia and autism. A study investigated the link between maternal *T. gondii* antibodies and the likelihood of autism in kids. The researchers tested IgG antibodies to particular infections, including *T. gondii*, in newborn blood samples from people later diagnosed with autism and controls. Because the neonate's IgG antibody is largely obtained from the mother, it can be used as a marker for maternal IgG (24). Toxoplasmosis IgG positive was found to be 2.9 percent in the ASD group and 2 percent in the control group in a study conducted in Turkey (26). Autism is caused by a combination of genetic and environmental factors. Toxoplasmosis interferes with an infant's genetics and may lead to autism, according to a study. The *T. gondii* interactome genes were significantly enriched in the susceptibility gene databases for all illnesses (25).

According to a recent study, fetal toxoplasmosis infection impairs electron transport chain genes (complexes I and III), which play a key role in free radical generation and oxidative stress production, contributing to the pathophysiology of neurodegenerative and neurodevelopmental disorders such as autism (5).

Autism sufferers' dopamine levels were discovered to be greater than usual. During latent toxoplasmosis, this neurotransmitter is connected to testosterone hormone, and both are increased. As a result, dopamine levels grow in tandem with testosterone levels. Dopamine synthesis can be boosted by nitric oxide and other inflammatory cytokines including Interleukin-2 (IL- 2) and IL-6. According to a study, the content of dopamine in the brains of mice with chronic toxoplasmosis is 14% greater than in the control group (27).

According to a study, autistic children exhibited a much higher seroprevalence of chronic toxoplasmosis than healthy controls. Toxoplasma-positive autistic children had considerably greater serum IFN- and NO concentrations than Toxoplasma-free children. It was discovered that the values of these two biomarkers have a substantial correlation. Latent chronic toxoplasmosis could have a long-term deleterious impact on CNS development since these metabolic abnormalities are linked to oxidative stress (27).

Patients with autism have significantly increased levels of several proinflammatory cytokines, chemokines, and differentiation factors in their brain tissue homogenates and cerebrospinal fluid. TNF-a levels in the CSF were substantially greater in children with autism than in other patients studied (means 104.10 pg/mL vs. 2.78 pg/mL). On average, the ratio of CSF TNF-a levels to serum TNF-a levels was 53.7:1. This could point to an inflammatory mechanism that contributes to autism development (28). In *T. gondii*-infected mice, *Miller et al.* showed that both CD4+ and CD8+ immunological T cells produced large levels of IFN-g in response to infected macrophages or tachyzoite lysate antigens (TLA), but the CD4+ T cells produced more of the cytokine with both stimulations. Both T cell types produced IL-2 after stimulation with

infected macrophages, but only CD4+ T cells did when stimulated with TLA (29). According to *Fond et al., T. gondii* tachyzoites may infect a variety of brain cells in the cerebellum, which then control signaling pathways and signal transduction mechanisms involved in a variety of functions such as cell apoptosis, immune cell maturation, and antimicrobial effector functions, which could lead to a variety of psychiatric illnesses, including autism (30).

Clinical manifestations

Acute infection is normally asymptomatic, but 10 to 20% of individuals develop bilateral, nontender lymphadenopathy in the cervical or axillary regions. A moderate flu-like condition with fever, malaise, myalgia, hepatosplenomegaly, and, less typically, pharyngitis might mimic infectious mononucleosis and include lymphadenitis in a few of these people. Common symptoms include atypical lymphocytosis, moderate anemia, leukopenia, and modestly increased liver enzymes. Most toxoplasmosis patients with AIDS or other immunocompromised individuals have encephalitis and ring-enhancing cerebral mass lesions seen on CT or MRI scans with contrast. These patients typically have headache, altered mental status, seizures, coma, fever, and sometimes focal neurologic deficits, such as motor or sensory loss, cranial nerve palsies, visual abnormalities, and focal seizures (31).

Ocular toxoplasmosis (OT) is characterized by localized, white retinal lesions that are often smaller than 1,000 microns in size, as well as a powerful vitreous inflammatory response that results in a distinctive 'headlight in the fog' image. Active lesions are frequently associated with contiguous old scars and are caused by both direct parasitic tissue invasion and the accompanying immune response aimed against the

parasite. Patients with AIDS have a unique presentation of the disease, with a wide range of clinical symptoms, and other infectious diseases such as CMV and syphilitic retinitis should be considered in the differential diagnosis (32).

Women who are infected with *T. gondii* before becoming pregnant seldom transmit the parasite to their fetus, but those who become acutely infected or have *T. gondii* reactivation during pregnancy (e.g., due to immunosuppression) can transmit the parasite transplacentally. When maternal infection occurs during the first trimester, the risk of congenital illness is lowest (10 to 25%) and highest (60 to 90%) when maternal infection occurs during the third trimester. When infection occurs during the first trimester, however, congenital illness is more severe (33).

In different parts of the world, congenital *T. gondii* infection is highly frequent, Congenital toxoplasmosis can cause a variety of symptoms, ranging from mild chorioretinitis that can appear years after birth to miscarriage, mental retardation, microcephaly, hydrocephalus, and seizures (34).

Epidemiology of toxoplasmosis

Toxoplasmosis is one of the most common infections in humans and warm-blooded animals, with a worldwide distribution. It has been demonstrated in virtually every species of mammal and many species of birds. In humans, toxoplasmosis has been found in all parts of the world and it is estimated about one-third of the worlds population is infected with latent toxoplasmosis. The incidence of toxoplasmosis differs, however, with underdeveloped countries having a higher incidence than developed countries. Areas of high prevalence exist in Latin America, parts of Eastern/Central Europe, the Middle East, and parts of south-east

Asia and Africa. In the US, seroprevalence is 15 to 22% (CDC), a slight drop from the preceding decade, consistent with the same trend in Europe. This variation in prevalence can be explained by several factors including the number and presence of the cats, climate, cultural and ethnic practices. Direct contact with cats is not required for transmission due to the longevity of oocysts in the environment (35).

It's a common parasite in Arabic region. According to recent study, approximately one-third of the population in Saudi Arabia had IgG seropositivity, and 6.4% had IgM seropositivity (36).

There is increase in the seroprevalence of toxoplasmisis in Iraq. According to a study done in the middle and northern regions in Iraq, the high prevalence of toxoplasmosis among the investigated high risk women at Al-Hawija and at Al-Baiji districts is due to many risk factors including age, number of deliveries, contact with host animals (37).

There is increased rate of the infection in Baghdad, a study conducted on pregnant women in Baghdad province, showed that the rate of infected women with toxoplasmosis (67%; while (33%) for women were no infected. The results recorded most commonly percent (53%) of women those who had one previous abortion and lesser percent (3%) for those who had a previous three or more abortion (38).

Also, there is increased prevalence of toxoplasmosis in Diyala province. A recent study conducted on 500 samples from Baquba city showed that the percentage of positive reactors recorded by LAT test were 41 % (39).

Diagnosis

The detection of *T. gondii* in fecal, water, environmental and tissue samples has traditionally relied on microscope examination. However,

identification based on light microscopy alone is less sensitive and unreliable. The oocysts in fecal, water and environment can be enriched from large volumes of samples by filtration or centrifugation for examination, and the tissue cysts can be stained, which helps to distinguish the parasites from host cells. Giemsa and Haematoxylin and Eosin (HE) staining is simple and cost-effective, and commonly used for this purpose (40).

The isolation of *T. gondii* by bioassay using laboratory animals is generally considered as the gold standard for detection of *T. gondii* infection. Secretions, excretions, body fluids, lymph nodes, muscle and brain tissues are possible specimens used for the isolation. Mice and cats are commonly used for bioassay of *T. gondii* (41).

Serological studies such as Latex Agglutination test has been used to detect anti-*T. gondii* IgM antibodies in humans for diagnosis of recent infection. *Sato* et al. isolated microsomal antigen Sp-2 reactive with anti-*T. gondii* antibodes, whose reactivity with IgM and IgG antibodies varies with the concentration. Sp-2 antigen only reacts with IgM when latex particles are sensitized with less than or equal to 100 mg of this antigen/mg of particles. Based on this unique reaction of the antigen, a passive latex agglutination reaction to detect IgM antibodies has developed (42).

ELISA has been used to detect the parasite. The test is used to detect anti-*T. gondii* IgG, IgM, and IgA antibodies rather than antigens, depending on the enzyme-linked antibody type. The conventional indirect ELISAs using tachyzoite lysate antigen (TLA) as coating antigen show a high degree of agreement with DT, MAT or IFAT detecting IgG or IgM antibodies in humans and animals (43).

Prevention

In most regions of the world, the main source of infection is undercooked meat with live tissue cysts. Other prominent causes of infection in areas with poor water hygiene include ingestion of oocyst-contaminated soil and water, as well as contact with infective oocysts. Recent research has found that oocyst infection is more essential than previously considered. Toxoplasmosis prevention is mostly focused on health education on minimizing personal exposure to the parasite. Many countries have implemented education programs targeted at lowering congenital toxoplasmosis rates. Development of an effective vaccine against *T. gondii* appears to be an achievable goal, as primary infection results in a life-long protection against the parasite. The most effective approach for vaccine development has been the use of non-virulent mutated strains of the parasite (3).

Conclusion

According to the studies we mentioned above, there is a high risk of getting autism after congenital toxoplasmosis but no definite clue was found. There is no definite evidence about the relationship between the toxoplasmosis and incidence of autism but there are many clues that need further investigation in future.

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