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Review

Congenital toxoplasmosis: An overview of the neurological and ocular manifestations

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ABSTRACT

Toxoplasma gondii is an obligate intracellular parasite which is known to infect one-third of the total world population chronically though it is asymptomatic in immunocompetent patients. However, in an immunocompromised patient or an infected fetus, it may cause devastating effects. The parasite may cross the placenta of an infected pregnant woman and probably infect the fetus congenitally. The severity of the infection depends on the gestational age at which the infection has occurred i.e., if it has occurred in the early phase, the rate of transmission is low but the severity is high if the fetus is infected and if it has occurred in the later phase then transmission rate is higher while the severity would be low. Congenital toxoplasmosis may result in non-specific consequences like abortion, intra-uterine growth restriction, jaundice, hepatosplenomegaly or even intra-uterine death. It may also result in neurological or ocular manifestations like intracranial calcifications, hydrocephalus or retinochoroiditis. The diagnosis may be done by serological screening of anti-*Toxoplasma* antibodies (IgM and IgG) while PCR of the amniotic fluid or the placenta is the confirmatory test. Acute or chronic infections may be differentiated by IgG avidity tests. The treatment regimens include spiramycin to prevent congenital transmission from an infected mother, pyrimethamine, sulfadoxine and folinic acid to treat the infected fetus, CSF shunting for the treatment of hydrocephalus and a combination of pyrimethamine, azithromycin, and corticosteroids for treating ocular toxoplasmosis.

1. Introduction

Toxoplasma gondii being a zoonotic, obligate intracellular protozoan parasite has the potential to infect all warm-blooded animals infecting almost one-third of world's population [1]. Toxoplasmosis is considered as one of the most important food borne inflammatory illnesses, associated with congenital abnormalities [2]. Felids serve as the definitive hosts for the parasite and it undergoes sexual reproduction in their gut. Environmentally resistant oocysts are released in the feline feces. These oocysts become highly infectious when they undergo sporulation in the soil under favorable conditions [3–5]. When they are accidentally ingested by mammals, they develop into tachyzoites which then get disseminated in blood to infect all tissues primarily the CNS, eyes, muscles, and placenta [6]. Tachyzoite infects nucleated host cells and utilizes the macrophages, dendritic cells and monocytes to evade the host immune defense and bypass the blood-brain barrier and the placenta barricade so that it could spread and form systemic disease [7, 8]. Fig. 1 shows the common mode of infection of *Toxoplasma gondii*.

Toxoplasmosis is considered as the second major cause of food borne deaths in the United States [9]. More than 80% of adults and children infected with *T. gondii* are asymptomatic. However, in case of immunodeficient patients, toxoplasmosis is a serious and life-threatening disease. An immunocompetent person with acute toxoplasmosis may show the following symptoms: cervical, retroperitoneal and mesenteric lymphadenopathy, malaise, fever, and myalgias. Retinochoroiditis has also been reported.

Acute toxoplasmosis in those patients who are immunodeficient but do not have AIDS show additional symptoms which are mainly neurological manifestations. These symptoms may include seizures, headache, cranial nerve deficit, focal neurologic deficit, disequilibrium, encephalitis, meningoencephalitis. Pneumonitis and myocarditis have also been reported. In such cases, the infection may be newly acquired or it may be a reactivation. However, in case of reactivation of the infection, symptoms are dependent only on the tissue or organ infected.

The commonly occurring manifestation of toxoplasmosis in patients with AIDS is toxoplasmic encephalitis with or without focal CNS lesions. The clinical findings are similar to those of immunodeficient patients without AIDS. Approximately, 58–89% of the cases show a subacute onset with focal neurologic abnormalities while 15–25% of the patients show more abrupt clinical presentation with seizures or

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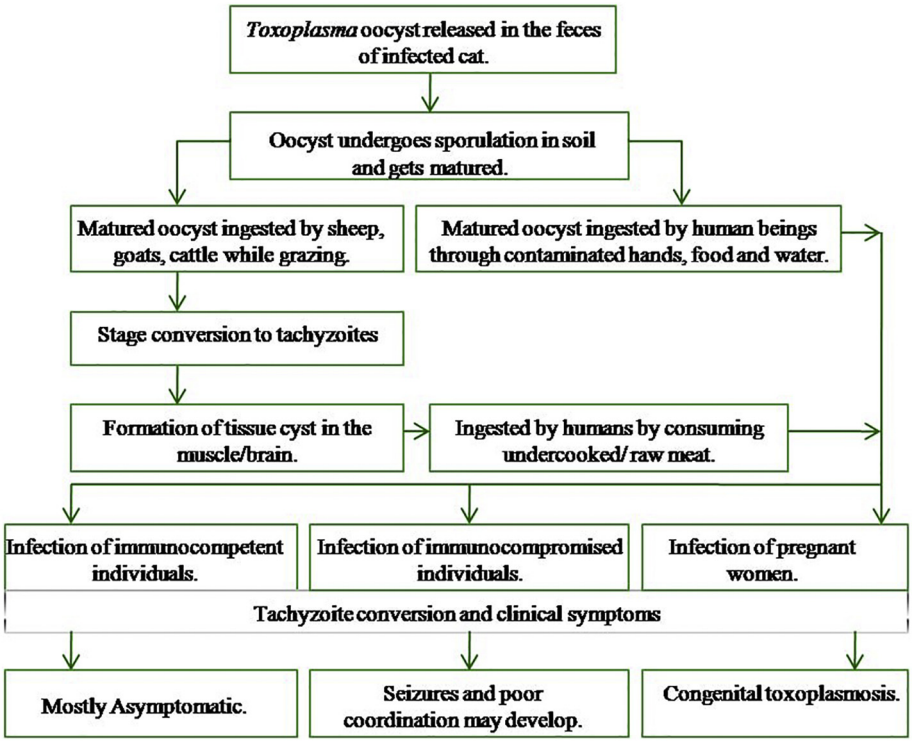

Fig. 1. Common mode of infection of *Toxoplasma gondii*.

cerebral hemorrhage. Diffuse toxoplasmic encephalitis may also develop. Motor or sensory disturbances of single or multiple limbs may be a result of the spinal cord involvement. Patients with AIDS who do not receive proper anti-HIV drugs or primary prophylaxis for toxoplasmosis may show pulmonary toxoplasmosis. Ocular toxoplasmosis mainly manifests as loss of visual activity and ocular pain while retinochoroiditis is comparatively less common in patients with AIDS. Diabetes insipidus, panhypopituitarism, abdominal pain and diarrhea (in case of gastrointestinal system invasion) may be some of the uncommon symptoms [10].

Congenital toxoplasmosis is caused when *Toxoplasma gondii* infects the fetus transplacentally. Tachyzoites bypass the placental blood barrier of the acutely infected mother and get transmitted to the fetus thereby compromising the fetal developmental process [4]. The seroprevalence of this infection differs from country to country or region to region within a given country [11]. In the United States, an estimated 22.5% population, 12 years or older have been infected with *Toxoplasma gondii*. This parasite is prevalent throughout the world with the incidence as high as 95% in some populations. Infection is highest in those regions of the world that have hot, humid climates and low altitudes [12]. In India, the exact seroprevalence of toxoplasmosis is unknown. Nevertheless, with the use of diverse diagnostic tests, the prevalence has been reported to be as low as 5% and as high as 80% in adults [13]. According to the recent reports of World Health Organisation, the incidence of congenital toxoplasmosis changes in accordance with the seropositivity of the population. The WHO report suggests that in case of high infection pressure, the proportion of women of childbearing age that is susceptible to the infection is low since most of them must have already been exposed. Therefore, even though seronegative women are at greater risk, the population that is actually at risk is low overall. When infection pressure is low, the opposite is the case [14]. The outcomes of congenital transmission of the parasite to a fetus are devastating [11]. Congenital toxoplasmosis may be subclinical, or present with multisystem involvement. Clinical manifestations, if present, include prematurity, intrauterine growth restriction, jaundice, hepatosplenomegaly, myocarditis, pneumonitis, purpura, chorioretinitis, hydrocephalus, intracranial calcifications, microcephaly, seizures, mental retardation, blindness and epilepsy [15]. Usually, the cases that are symptomatic show either ocular or neurological manifestations [16]. Our study deals with general review of the clinical manifestations of toxoplasmosis with more emphasis on the neurological manifestations, its diagnosis, and the treatment.

2. Clinical manifestations of congenital transmission

Congenital toxoplasmosis can be evident with harsh outcomes ranging from spontaneous fetal loss, death in utero, intra uterine growth retardation, hydrocephalus, encephalitis, neurological mental illness, ocular damage like retinochoroiditis, auditory and inflammatory disorders, cardiovascular abnormalities, or a healthy infant without any symptoms of congenital toxoplasmosis [17, 18]. Even though clinical signs are not present in most children at birth, they can emerge at any time [19]. Central Nervous System and ocular disease in the first three months of life can be seen in case of premature infants infected with *T. gondii*. However, if the infected infant is full-term, the disease is usually milder with lymphadenopathy and hepatosplenomegaly in the first two months of life [20]. Congenital toxoplasmosis may occur as a disease of the neonate or a subclinical infection. If the disease is recognized clinically in the newborn, it may be very severe resulting in eosinophilia, cerebral calcifications, abnormal cerebrospinal fluid, jaundice, enlargement of the spleen and/or liver, lymphadenopathy. Neurological signs that may accompany include nystagmus, micro or macrocephaly, bulging fontanelle, seizures and abnormal muscle tone [21]. Increase in the cerebrospinal fluid protein levels (> 1 g/dl) leads to the obstruction of the Aqueduct of Sylvius causing obstructive hydrocephalus which results in the third ventricle dilation while obstruction of the Foramen of Monroe results in the unilateral or bilateral ventricular dilatation. However, hydrocephalus has also been reported to