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Toxoplasma gondii

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Toxoplasma gondii is an obligate intracellular parasite that infects up to a third of the world's population and causes a disease known as toxoplasmosis. Infected individuals are rarely symptomatic, as the immune system usually keeps the parasites at bay. However, primary infection may present in some patients with lymphadenopathy or ocular disease. If toxoplasmosis is acquired during pregnancy it may cause severe damage to the fetus. In immunocompromised patients, reactivation of latent toxoplasmosis can cause life-threatening encephalitis. Diagnosis is usually performed by serological techniques or by direct detection of the parasite.[1]

Background

Toxoplasma gondii is a member of the phylum Apicomplexa. Within the species *T. gondii*, there are three dominant strains (types I, II and III) which have evolved from sexual recombination in definitive hosts. Types I and II have been identified in human infections; however, the full genetic diversity of *T. gondii* in humans is unknown.[2] The parasite can also take on numerous forms: the oocyst, the tachyzoite, and the cyst.

Every member of the cat family, from domestic pets to mountain lions, serve as definitive hosts for *T. gondii* and are required for completion of the sexual cycle. Replication of the parasite occurs in the cat's intestinal tract, where several million oocysts are produced and shed in the feces for 7-21 days during the course of an acute infection.[3] These oocysts are transmitted from cats to various warm-blooded vertebrate species. Each infected host excretes large numbers of encysted parasites, of which only a few are required to initiate infection. The oocysts are small, buoyant, resistant to most disinfectants, and can survive in moist environments for months, allowing for rapid and widespread dispersal, especially after rainfalls.[4] Rainfall-initiated runoff from landscapes and wastewater outfalls carry the protozoa into untreated waters used for agriculture, recreation and, in some regions, for drinking. In addition, *T. gondii* are also present in coastal waters, contaminating shellfish and infecting many marine mammals.[2]

Upon sporulation, oocysts containing sporozoites are infective when ingested by mammals and give rise to the tachyzoite stage. Tachyzoites are oval or crescent-shaped and proliferate rapidly. They are capable of entering all nucleated cells by active penetration, forming a cytoplasmic vacuole within the cell.[5] Inside the cytoplasm, rapid replication ensues, disrupting the host cell and releasing the tachyzoites upon cell death. Once in the bloodstream, tachyzoites are disseminated throughout the body and infect numerous tissues, including the CNS, eye, heart, skeletal muscle, and placenta. Tachyzoites are the form of the parasite that cause clinical manifestations of toxoplasmosis, as the tachyzoite evokes a strong inflammatory response and tissue destruction ensues. However, under the relentless pressure of a competent immune system, tachyzoites transform into bradyzoites to form cysts.[1]

Bradyzoites are morphologically identical to tachyzoites but multiply very slowly. They are also functionally different, persisting within cysts for the life of the host. Tissue cysts contain thousands of bradyzoites and form within muscle and brain tissue. Cysts are considered the infective forms for intermediate and definitive hosts. Bradyzoites can be released from cysts and revert back to tachyzoites, causing infection. This is commonly seen in immunocompromised patients.[1,2]

Transmission

There are three well-known routes of transmission of *T. gondii*. These include transmission through oocysts shed in the feces of wild and domestic cats, ingestion of tissue cysts from infected meats (mainly pork and lamb), and congenital transmission. Needle-stick injuries and organ transplantation have also been found to transmit *T. gondii*.[1] Many routes of exposure are possible; however, oocyst transmission is the most common, as oocysts are the only form capable of remaining infectious in the environment for up to a year while being disseminated in large numbers.[6] Transmission of *T. gondii* via organ transplantation from a seropositive donor to a seronegative recipient has recently been identified as an important cause of disease in heart, lung, kidney, and liver transplant patients, due to reactivation of the latent infection in the recipient.[7]

Pathogenesis

Inoculum size, virulence factors, genetic background, sex and immunological status affect the outcome of toxoplasmosis infection in humans.[8-11] Once ingested, the parasite actively invades

intestinal epithelial cells or is phagocytosed by them.[12] The cytoplasmic vacuoles induced by *T. gondii* exclude host proteins that would promote phagosome maturation, thereby preventing lysosome fusions.1 Infection with *T. gondii* causes a strong and persistent T_H1 response, with the production of pro-inflammatory cytokines (IL-12, IFN-γ, and TNFα). Within two weeks of infection, IgG, IgM, IgA, and IgE antibodies against *T. gondii* proteins can be detected. The production of IgA on mucosal surfaces appears to protect the host from reinfection.[13,14]

Clinical Presentation

Clinically, infection with *T. gondii* may go unnoticed or can be symptomatic, depending on the immune status of the patient and the clinical setting. Primary infection in most immunocompetent children, adults, and pregnant women is asymptomatic. However, about 10% of patients will complain of flu-like symptoms that are self-limiting and rarely require treatment.[1] The most typical clinical manifestation is isolated, non-tender, cervical, or occipital lymphadenopathy, with reticular cell enlargement or hyperplasia. Very infrequently myocarditis, polymyositis, pneumonitis, hepatitis, or encephalitis caused by tissue necrosis can arise in otherwise healthy individuals.[15]

Retinitis is associated with proliferation of *T. gondii* within cells of the retina. This is usually seen in the setting of congenital or postnatal toxoplamosis, as the result of acute infection or reactivation.[16] White focal lesions with an overlying and intense vitreal inflammatory reaction are typical clinical findings. The classic "headlight in the fog" appearance is attributed to the presence of active retinal lesions with a severe inflammatory reaction.[1,17]

In immunocompromised or immunosuppressed individuals, *T. gondii* frequently results in fatal disseminated disease with heavy cerebral involvement. In these individuals, toxoplamosis is almost always the result of reactivation of a chronic infection.[18] Toxoplasmosis has recently become a major cause of mortality in AIDS patients from a unique encephalitis with necrotizing lesions accompanied by inflammatory infiltrates.[15] Clinical manifestations include mental status changes, seizures, focal motor deficits, cranial nerve disturbances, sensory abnormalities, cerebellar symptoms, movement disorders, and neuropsychiatric findings. The most typical focal neurological findings are hemiparesis and speech abnormalities.[19] The differential diagnosis of toxoplasmic encephalitis lesions includes CNS lymphoma, progressive multifocal leukoencephalopathy, CMV ventriculitis and encephalitis, and focal lesions caused by other organisms including *M. tuberculosis* and *Aspergillus spp*, or bacterial brain abscess.[1]

Neonatal clinical manifestations in congenital toxoplamosis have wide variability, and may include hydrocephalus, microcephaly, intracranial calcifications, chorioretinitis, strabismus, blindness, epilepsy, psychomotor or mental retardation, petechiae due to thrombocytopenia and anemia.[20] However, none are pathognomonic for congenital toxoplamosis and many can be mimicked by congenital infection with other pathogens, including CMV, herpes simplex virus, rubella, and syphilis.[21]

Diagnosis & Treatment

T. gondii infection can be diagnosed indirectly with serological methods, such as detection of IgG antibodies to *T. gondii* and directly by PCR, hybridization, isolation, and histology. Direct demonstration of the organism is possible through mouse inoculation, cell culture, or PCR for *T. gondii* DNA from cerebrospinal fluid (CSF), blood and urine. Ophthalmologic testing, radiological studies, and examination of CSF usually assist the diagnosis of disease, mainly in congenital toxoplasmosis.[1,21]

Treatment of toxoplasmosis involves a combination of pyrimethamine (Daraprim), sulfadiazine and folinic acid. Treatment is usually administered for four weeks followed by a reassessment of the patient's condition. Prevention and control of infection requires minimizing exposures by avoiding the consumption of raw meat and eggs, washing hands after working in the soil, cleaning cat litter boxes on a daily basis, and keeping any personal cats indoors and feeding them only commercial foods.[15]

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