Toxoplasmosis: A Global Threat

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ABSTRACT

Toxoplasmosis, a disease described worldwide, which is caused by the protozoan *Toxoplasma gondii,* commonly involves the retina. The disease has a higher impact in immunocompromised individuals and in congenital infection because of the severity of central nervous system involvement. Although simple prophylactic measures could reduce transmission, *T. gondii* seroprevalence is still high, especially in South America. Educational campaigns and the development of new drugs to prevent primary infection could potentially reduce the burden of the disease.

Key words: Congenital toxoplasmosis, Ocular toxoplasmosis, Toxoplasmic encephalitis

INTRODUCTION

Toxoplasmosis, caused by the protozoan *Toxoplasma gondii,* causes a retinal infection, affecting healthy and immunocompromised people in many countries;[1] and it can also be a life-threatening disease in immune-suppressed individuals.[2] The parasite is transmitted through raw meat containing *T. gondii* cysts or water containing oocysts from feline feces.[3] Both waterborne[4-7] and food-borne[8] outbreaks of the disease have been reported from countries with diverse cultural, social and ethnic backgrounds. The parasite can be transmitted vertically as well, mainly when women acquire primary disease during pregnancy.[9] Although rare, the disease can also be transmitted through transplanted organs.[10]

Although felines are the only definitive host, *T. gondii* can infect and replicate within virtually any nucleated vertebrate cell.[11] The *T. gondii* life cycle is divided into two parts: an asexual phase, which takes place in nucleated cells; and a sexual phase within the gastrointestinal tract of cats.[11] Fertilized gametes are generated from sexual replication within the feline's small intestine, and excreted oocysts can last in the environment for 18 months.[12]

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Once ingested, oocysts and/ or tissue cysts rupture and invade cells in intestinal lining, and the sporozoites (released from the oocysts) or the bradyzoites (released from the tissue cysts) differentiate into tachyzoites, the fast-replicating form of the parasite.[13] These tachyzoites may be detected in host leukocytes or may be circulating freely within the bloodstream.[14-16]

T. gondii exists in clonal populations.[17] Initially three clonal types were designated based on genotype similarities, named type I, type II and type III; however, some strains formerly classified as "atypical" were recognized as different haplogroups based on phylogenetic analysis, and currently more haplogroups are described.[18]

EPIDEMIOLOGY OF HUMAN INFECTION

Worldwide, over 6 billion people have been infected with *T. gondii*.[19] Seroprevalence, measured by IgG against *T. gondii,* varies worldwide, being reported to be 6.7% in Korea,[20] 12.3% in China,[21] 23.9% in Nigeria,[22] 46% in Tanzania[23] and 47% in France (rural area),[24] and can be as high as 98% in some regions.[25]

In the United States, prevalence of Toxoplasmosismay be declining, but approximately 14% of the individuals are seropositive by the age of 40 years,[26] with one million new infections each year, resulting in approximately 20,000 cases of retinal infection[27] and 750 deaths, making it the

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second most common cause of deaths related to food-borne diseases.[28]

South America and Africa have a bigger variety of haplogroups than North America and Europe,[18,29] suggesting that in these continents sexual replication of the parasites occurs more frequently than in any other part of the world. This variety may contribute to the higher prevalence of seropositivity and ocular disease due to *T. gondii,*[30] because in South America, toxoplasmic eye disease and infection prevalence is higher than in many other parts of the world.[31] Environmental conditions, eating habits, hygiene and host susceptibility may also contribute to the differences in prevalence found globally.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The majority of the immunocompetent subjects will remain asymptomatic lifelong, but both competent and immunocompromised subjects can develop the disease, especially retinochoroiditis. Infected individuals may present with asymptomatic cervical lymphadenopathy during the acute systemic infection; as well as signs and symptoms that mimic mononucleosis infection, like myalgia, sore throat, fever, maculopapular rash and, infrequently, polymyositis and myocarditis.[12]

Ocular toxoplasmosis

Ocular toxoplasmosis (OT) generally causes characteristic looking retinal lesions that are focal and white, which are usually smaller than 1,000 microns in size,[32] with a vigorous vitreous inflammatory reaction resulting in a typical 'headlight in the fog' appearance.[13] These lesions are due both to direct parasitic tissue invasion and the ensuing immune response directed against the parasite;[33] and active lesions are often associated with contiguous old scars.[34] Patients with AIDS have a different presentation of the disease, with a broad variety of clinical signs,[35] and the differential diagnosis should include other infectious diseases, such as cytomegalovirus and syphilitic retinitis.[1]

Retinochoroidal inflammation during a primary or recurrent eye infection generally persists for 2 to 4 months.[34] In an observational case series comprising 154 patients with active OT lesions followed for at least 5 years, it was found that almost one patient out of four developed blindness in at least one eye; and one out of five patients had recurrences, mainly in eyes with previous retinal scars.[36] The risk of recurrence of OT is higher in individuals aged 40 or more, and also within 5 years after the most recent episode.[37]

Toxoplasmic encephalitis

Even in this era of highly active antiretroviral therapy, toxoplasmic encephalitis (TE) is a leading cause of morbidity and mortality in AIDS patients,[2] and is usually caused by reactivation of a latent infection.[38] A wide range of nonspecific symptoms, such as dementia, ataxia, lethargy, seizures, can be present, which makes the clinical diagnosis difficult to make,[39] and TE should be suspected, especially in areas with a higher prevalence of the disease, like South America.

Although not pathognomonic, the presence of multiple brain abscesses is the most typical feature of *T. gondii* infection in AIDS patients. Postmortem brain analyses describe a global involvement of both hemispheres, although the basal ganglia and the corticomedullary junction are the commonest sites of *T. gondii* brain infection.[38]

Congenital toxoplasmosis

Newborns presenting with congenital toxoplasmosis can be asymptomatic but can also develop retinochoroiditis and/ or CNS involvement.[40] It is estimated that prevalence of congenital toxoplasmosis is 1-10 per 10,000 live births in United States,[41] one per 770 live births in Southeast Brazil[42] and one per 3,000 live births in France.[43] Although hard to estimate, the burden attributed to the disease in Netherlands is approximately 620 disability-adjusted life years (DALYs) annually, mainly due to retinal disease and fetal loss.[44] This burden is comparable to that of the well-known and frequent food-borne pathogen *Salmonella spp.*[45]

The risk of vertical transmission is higher at later stages of pregnancy, but infection is usually more severe if transmitted early in the gestation period.[9]

Intracranial calcifications may be present and are detected by ultrasonography. Clinical signs and symptoms include hydrocephalus, delayed mental development and/ or epilepsy, which may mimic other congenital infections of the TORCH complex (i.e., rubella, cytomegalovirus, herpes simplex virus).[13]

Congenital OT is generally more sight-threatening than acquired infections, as retinal lesions found in congenitally infected newborns are often placed in the macula,[36] the region responsible for central vision, and children presenting with toxoplasmosis-related blindness or low vision will live many years with the disability.

In the United States, approximately 9% of children with congenital toxoplasmosis have significant visual

impairment,[46] whereas rates are much higher in other regions. Within Europe, 29% of such children have visual impairment, compared with 87% from the Brazilian cohorts, in the three to four years following birth.[47]

Laboratory diagnosis

Detection of prior infection can be documented by serology, with changes in serology used to infer acute infection. The IgG response generally appears within 7 to 14 days of infection, has a peak within 30 to 60 days and usually persists lifelong.[48]

IgM appears prior to IgG after primary infection but typically do not persist, and if present, indicate acute infection; but confirmatory tests should be executed, as its specificity is not always satisfactory. By testing the avidity for *T. gondii* IgG, one can discriminate whether the infection was acquired recently or in the past,[48] as in a small percentage of the cases *T. gondii* IgM can remain positive for up to 24 months.[49]

Other methods that may also be used to assess the disease are the histology of infected tissues, polymerase chain reaction (PCR) of body fluids (like cerebrospinal fluid), or culture of the parasite. For prenatal diagnosis, PCR to detect parasite DNA on amniotic fluid should be performed.[48] PCR of aqueous humor and/ or vitreous can be an important tool to diagnose OT with atypical presentation in AIDS patients.[50]

TREATMENT AND PREVENTION

Hygienic measures can reduce the transmission of the parasite, such as washing fruits and vegetables, avoiding consumption of raw and undercooked meat, and washing hands after gardening or handling cats.[41] Although these measures are cost-effective and easily implemented, in some areas water used for washing may be contaminated with toxoplasmosis.[51] Many pregnant women are unaware that toxoplasmosis can be transmitted through uncooked meat, for example;[52] and educative campaigns should be devised to help prevent the transmission of the disease.

Treatment of TE in AIDS patients consists of pyrimethamine, sulfadiazine and folinic acid, with clindamycin used as an alternative in patients allergic to sulfadiazine. Prophylaxis against TE is indicated in IgG-positive patients with less than 100 CD4 T lymphocytes per mm^3, and consists of trimethoprim-sulfamethoxazole.[38] Patients taking pyrimethamine must have their blood cells regularly monitored, as the drug can potentially cause bone marrow depression.[9]

Although there are an immense number of varieties of different therapies to treat acute or recurrent OT, a combination of sulfadiazine, pyrimethamine, folinic acid and oral prednisone is the commonest therapy prescribed by ophthalmologists.[33] Short-term therapy of OT does not prevent disease recurrence, although prolonged suppressive therapy with sulfamethoxazole and trimethoprim can reduce the number of recurrences.[53] It is important to emphasize that there is no treatment that restores damaged retinal cells, and both active lesions and scars can lead to permanent blindness.

CONCLUSION

Although most immunocompetent individuals infected with toxoplasmosis remain asymptomatic throughout life, worldwide this parasite causes a large amount of visual loss and morbidity, in addition to fatal infections in immunocompromised patients. Hygienic measures are cost-effective and can reduce the chance of transmission, and new studies should be directed towards prevention of primary infection.

REFERENCES

1. Holland GN, O'Connor RR Jr, Remington JS. Toxoplasmosis. In: Pepose JS, Holland GN, Wilhelmus KR, editors. Ocular Infection and Immunity. St. Louis: Mosby-Year Book, Inc; 1996. p. 1183-223.
2. Contini C. Clinical and diagnostic management of toxoplasmosis in the immunocompromised patient. Parassitolog 2008;50:45-50.
3. Jones JL, Dubey JP. Waterborne toxoplasmosis-recent developments. Exp Parasitol 2010;124:10-25.
4. Bowie WR, King AS, Werker DH, Isaac-Renton JL, Bell A, Eng SB, *et al.* Outbreak of toxoplasmosis associated with municipal drinking water: The BC Toxoplasma Investigation Team. Lancet 1997;350:173-7.
5. Palanisamy M, Madhavan B, Balasundaram MB, Andavar R, Venkatapathy N. Outbreak of ocular toxoplasmosis in Coimbatore, India. Indian J Ophthalmol 2006;54:129-31.
6. Balasundaram MB, Andavar R, Palaniswamy M, Venkatapathy N. Outbreak of acquired ocular toxoplasmosis involving 248 patients. Arch Ophthalmol 2010;128:28-32.
7. de Moura L, Bahia-Oliveira LM, Wada MY, Jones JL, Tuboi SH, Carmo EH, *et al.* Waterborne toxoplasmosis, Brazil, from field to gene. Emerg Infect Di 2006;12:326-9.
8. Choi WY, Nam HW, Kwak NH, Huh W, Kim YR, Kang MW, *et al.* Foodborne outbreaks of human toxoplasmosis. J Infect Dis 1997;175:1280-2.
9. Montoya JG, Remington JS. Management of *Toxoplasma gondii* infection during pregnancy. Clin Infect Dis 2008;47:554-66.
10. Derouin F, Pelloux H. Prevention of toxoplasmosis in transplant patients. Clin Microbiol Infect 2008;14:1089-101.
11. Black MW, Boothroyd JC. Lytic cycle of *Toxoplasma gondii*. Microbiol Mol Biol Rev 2000;64:607-23.
12. Montoya JG, Remington JS. *Toxoplasma gondii*. In: Mandell GL, Bennett JE, Dolin RF, editors. Principles and Practice of Infectious Diseases. 5th ed. Philadelphia: Churchill Livingstone; 2000. p. 2858-88.
13. Montoya JG, Liesenfeld O. Toxoplasmosis. Lancet 2004;363:1965-76.
14. Courret N, Darche S, Sonigo P, Milon G, Buzoni-Gatel D, Tardieux I. CD11c- and CD11b-expressing mouse leukocytes transport single *Toxoplasma gondii* tachyzoites to the brain. Blood 2006;107:309-16.

15. Lambert H, Hitziger N, Dellacasa I, Svensson M, Barragan A. Induction of dendritic cell migration upon *Toxoplasma gondii* infection potentiates parasite dissemination. Cell Microbiol 2006;8:1611-23.
16. Silveira C, Vallochi AL, Rodrigues da Silva U, Muccioli C, Holland GN, Nussenblatt RB, *et al*. *Toxoplasma gondii* in the peripheral blood of patients with acute and chronic toxoplasmosis. Br J Ophthalmol 2011;95:396-400.
17. Sibley LD, Boothroyd JC. Virulent strains of *Toxoplasma gondii* comprise a single clonal lineage. Nature 1992;359:82-5.
18. Khan A, Fux B, Su C, Dubey JP, Darde ML, Ajioka JW, *et al*. Recent transcontinental sweep of *Toxoplasma gondii* driven by a single monomorphic chromosome. Proc Natl Acad Sci U S A 2007;104:14872-7.
19. Klaren VN, Kijlstra A. Toxoplasmosis, an overview with emphasis on ocular involvement. Ocul Immunol Inflamm 2002;10:1-26.
20. Shin DW, Cha DY, Hua QJ, Cha GH, Lee YH. Seroprevalence of *Toxoplasma gondii* infection and characteristics of seropositive patients in general hospitals in Daejeon, Korea. Korean J Parasitol 2009;47:125-30.
21. Xiao Y, Yin J, Jiang N, Xiang M, Hao L, Lu H, *et al*. Seroepidemiology of human *Toxoplasma gondii* infection in China. BMC Infect Dis 2010;10:4.
22. Kamani J, Mani AU, Egwu GO, Kumshe HA. Seroprevalence of human infection with *Toxoplasma gondii* and the associated risk factors, in Maiduguri, Borno state, Nigeria. Ann Trop Med Parasitol 2009;103:317-21.
23. Swai ES, Schoonman L. Seroprevalence of *Toxoplasma gondii* infection amongst residents of Tanga district in north-east Tanzania. Tanzan J Health Res 2009;11:205-9.
24. Fromont EG, Riche B, Rabilloud M. Toxoplasma seroprevalence in a rural population in France: Detection of a household effect. BMC Infect Dis 2009;9:76.
25. Silveira C, Belfort R Jr, Burnier M Jr, Nussenblatt R. Acquired toxoplasmic infection as the cause of toxoplasmic retinochoroiditis in families. Am J Ophthalmol 1988;106:362-4.
26. Jones JL, Kruszon-Moran D, Sanders-Lewis K, Wilson M. *Toxoplasma gondii* infection in the United States, 1999-2004, decline from the prior decade. Am J Trop Med Hyg 2007;77:405-10.
27. Jones JL, Holland GN. Annual burden of ocular toxoplasmosis in the US. Am J Trop Med Hyg 2010;82:464-5.
28. Scallan E, Hoekstra RM, Angulo FJ, Tauxe RV, Widdowson MA, Roy SL, *et al*. Foodborne illness acquired in the United States-major pathogens. Emerg Infect Dis 2011;17:7-15.
29. Mercier A, Devillard S, Ngoubangoye B, Bonnabau H, Bañuls AL, Durand P, *et al*. Additional haplogroups of *Toxoplasma gondii* out of Africa: Population structure and mouse-virulence of strains from Gabon. PLoS Negl Trop Dis 2010;4:e876.
30. Khan A, Jordan C, Muccioli C, Vallochi AL, Rizzo LV, Belfort R Jr, *et al*. Genetic divergence of *Toxoplasma gondii* strains associated with ocular toxoplasmosis, Brazil. Emerg Infect Dis 2006;12:942-9.
31. Glasner PD, Silveira C, Kruszon-Moran D, Martins MC, Burnier Júnior M, Silveira S, *et al*. An unusually high prevalence of ocular toxoplasmosis in southern Brazil. Am J Ophthalmol 1992;114:136-44.
32. Holland GN. Ocular toxoplasmosis: A global reassessment. Part II: Disease manifestations and management. Am J Ophthalmol 2004;137:1-17.
33. Holland GN, Lewis KG. An update on current practices in the management of ocular toxoplasmosis. Am J Ophthalmol 2002;134:102-14.
34. Rothova A. Ocular manifestations of toxoplasmosis. Curr Opin Ophthalmol 2003;14:384-8.
35. Holland GN, Engstrom RE Jr, Glasgow BJ, Berger BB, Daniels SA, Sidikaro Y, *et al*. Ocular toxoplasmosis in patients with the acquired immunodeficiency syndrome. Am J Ophthalmol 1988;106:653-67.
36. Bosch-Driessen LE, Berendschot TT, Ongkosuwito JV, Rothova A. Ocular toxoplasmosis: clinical features and prognosis of 154 patients. Ophthalmology 2002;109:869-78.
37. Holland GN, Crespi CM, ten Dam-van Loon N, Charonis AC, Yu F, Bosch-Driessen LH, *et al*. Analysis of recurrence patterns associated with toxoplasmic retinochoroiditis. Am J Ophthalmol 2008;145:1007-13.
38. Luft BJ, Chua A. Central nervous system toxoplasmosis in HIV pathogenesis, diagnosis, and therapy. Curr Infect Dis Re 2000;2:358-62.
39. Luft BJ, Remington JS. Toxoplasmic encephalitis in AIDS. Clin Infect Dis 1992;15:211-22.
40. Montoya JG, Remington JS. Toxoplasmosis of the central nervous system. In: Pepose PK, Remington JS, editors. Defense of the brain: Current concepts in the immunopathogenesis and clinical aspects of CNS infections. Boston: Blackwell Scientific 1997. p. 163-88.
41. Lopez A, Dietz VJ, Wilson M, Navin TR, Jones JL. Preventing congenital toxoplasmosis. MMWR Recomm Rep 2000;49:59-68.
42. Vasconcelos-Santos DV, Machado Azevedo DO, Campos WR, Oréfice F, Queiroz-Andrade GM, Carellos EV, *et al*. Congenital toxoplasmosis in southeastern Brazil: Results of early ophthalmologic examination of a large cohort of neonates. Ophthalmology 2009;116:2199-205, e1.
43. Villena I, Ancelle T, Delmas C, Garcia P, Brezin AP, Thulliez P, *et al*. Congenital toxoplasmosis in France in 2007: First results from a national surveillance system. Euro Surveill 2010;24:15.
44. Havelaar AH, Kemmeren JM, Kortbeek LM. Disease burden of congenital toxoplasmosis. Clin Infect Dis 2007;44:1467-74.
45. Kemmeren J, Mangen M-J, Duynhoven YV, Havelaar A. Priority setting of foodborne pathogens-disease burden and costs of selected enteric pathogens. Report no. 330080001.: Bilthoven: National Institute for Public Health and the Environment; 2006.
46. Tan HK, Schmidt D, Stanford M, Teär-Fahnehjelm K, Ferret N, Salt A, Gilbert R, *et al*. Risk of visual impairment in children with congenital toxoplasmic retinochoroiditis. Am J Ophthalmol 2007;144:48-653.
47. Gilbert RE, Freeman K, Lago EG, Bahia-Oliveira LM, Tan HK, Wallon M, *et al*. Ocular sequelae of congenital toxoplasmosis in Brazil compared with Europe. PLoS Negl Trop Dis 2008;2:e277.
48. Montoya JG. Laboratory diagnosis of *Toxoplasma gondii* infection and toxoplasmosis. J Infect Dis 2002;185:S73-82.
49. Gras L, Gilbert RE, Wallon M, Peyron F, Cortina-Borja M. Duration of the IgM response in women acquiring *Toxoplasma gondii* during pregnancy: Implications for clinical practice and cross-sectional incidence studies. Epidemiol Infect 2004;132:541-8.
50. Moshfeghi DM, Dodds EM, Couto CA, Santos CI, Nicholson DH, Lowder CY, *et al*. Diagnostic approaches to severe, atypical toxoplasmosis mimicking acute retinal necrosis. Ophthalmology 2004;111:716-25.
51. Jones JL, Krueger A, Schulkin J, Schantz PM. Toxoplasmosis prevention and testing in pregnancy, survey of obstetrician-gynaecologists. Zoonoses Public Health 2010;57:27-33.
52. Jones JL, Ogunmodede F, Scheftel J, Kirkland E, Lopez A, Schulkin J, *et al*. Toxoplasmosis-related knowledge and practices among pregnant women in the United States. Infect Dis Obstet Gynecol 2003;11:139-45.
53. Silveira C, Belfort R Jr, Muccioli C, Holland GN, Victora CG, Horta BL, *et al*. The effect of long-term intermittent trimethoprim/sulfamethoxazole treatment on recurrences of toxoplasmic retinochoroiditis. Am J Ophthalmol 2002;134:41-6.

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