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Review Article

Toxoplasmosis: A Highly Complex Clinical Issue and a Diagnostic Challenge: Brief Overview

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Abstract

Toxoplasma gondii, a ubiquitous, compulsory, intracellular parasite was first discovered around 100 years ago. Toxoplasmosis, a common global zoonose, exhibits a marked variation of clinical manifestations, depending on the immune status of the host. In this regard, toxoplasma infection though usually latent in immune competent individuals, may cause severe disease, especially encephalitis, in the setting of immune suppression (acquired immune deficiency syndrome, solid organ transplantation, allogeneic hematopoietic stem cell transplantation-HSCT, immunosuppressive therapies). Noteworthy, cerebral toxoplasmosis has declined in view of widespread use of highly active antiretroviral therapy (HAART) in the cohort of AIDS patients. Congenital toxoplasmosis results almost solely from primary acquired maternal infection during gestation or from reactivation of latent infection in immunesuppressed pregnants. Chorioretinitis, hydrocephalus and intracranial calcifications consist the classic triad of symptoms. Ocular toxoplasmosis acquired either by congenital or postnatal routes, is the most common cause of posterior uveitis .This review is an effort to briefly summarize data on biological life cycle, trasmission routes of the parasite, as well as epidemiological, clinical, diagnostic features and aspects of toxoplasmosis in humans according to their immune background.

Keywords: Toxoplasmosis; Uveitis; Encephalitis; Congenital infection; Immunosuppression

Introduction

Toxoplasmosis is a parasitic disease with worldwide distribution caused by T. gondii, a compulsory intracellular protozoal parasite that infects most species of warm-blooded animals, including humans. Inside human body it virtually infects all nucleated cells [1]. T. gondii is a member of phylum Apicomplexa, and belongs to the coccidian subclass. Approximately, one third of the human population is infected by the parasite globally. Seroprevalence varies significantly though out the world between different geographic areas, population groups, and increases with age. Warm, humid climates and low altitudes appear to favor the infection. Apart from climatic factors, dietary habits (eating raw or undercooked meat), economic social factors, quality of water and sanitation coverage affect the prevalence rates [2,3]. Toxoplasmosis causes potentially life-threatening, opportunistic infection in the setting of immunosuppression, harboring a challenging clinical problem of major public health concern [4]. In contrast, in immunocompetent hosts, acute infection is typically asymptomatic and subclinical or causes mild, self-limited symptoms and signs.

Toxoplasmosis is categorized into four major groups: (1) congenital toxoplasmosis (CnT) (2) acquired toxoplasmosis in immunocompetent hosts, (3) ocular toxoplasmosis (OT), congenital or acquired and (4) cerebral toxoplasmosis (CT).

History

Though T. gondii was discovered in 1908 by two independent research groups (Nicolle and Manceaux in the North African rodent, Ctenodactulus gondii and by Splendor in rabbits in Brazil), its pathogenic potential was not recognized till 1920 in congenitally infected children [5,6]. In 1948, Sabin and Feldman developed the dye test, a serologic assay that has been the gold standard of diagnosis for many years [2,7]. During the same period (1951) Hogan reported the first detailed description of ocular toxoplasmosis [8]. In the 1960s, the cat was identified as the definitive host, clarifying the parasite's life cycle. Toxoplasmic encephalitis in immune compromised was first reported in 1967 in patients with Hodgkin disease during immunosuppressive therapies [8]. One year later, Remington et al suggested the role of the detection of IgM antibodies in the cord lord to the diagnosis of congenital toxoplasmosis [8]. In the 1980s, T. gondii emerged as a significant cause of mortality and morbidity in patients with acquired immunodeficiency syndrome [6].

Infectious Stages

The three infectious forms of T. gondii are: i) tachyzoite, rapidly multiplied in any cell of the intermediate host and in nonintestinal epithelial cells of the definitive host [9]. Tachyzoites replicate every 6-8h by endodyogeny and are found during acute infection [8,9], ii) a slowly growing stage of bradyzoite within a tissue cyst that predominates during chronic infection and iii). an environmental stage, the sporozoite protected inside an oocyst. Oocysts are excreted in cat feces [2,5].

Life Cycle

Definitive hosts for T. gondii are members of the family Felidae (domestic and wild cats-felidae), while humans and other mammals

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(all warm blooded animals including birds and mice) are intermediate hosts. T. gondii has a complex, biphasic life cycle with both sexual and asexual stages. Sexual reproduction occurs only in definitive host, that can be infected via consumption of oocysts or cysts shedding within tissues of intermediate hosts. Consequently, gastric enzymes destroy the cyst wall and the released bradyzoites invade the feline intestine. Parasites undergo cycles of asexual multiplication followed by sexual reproduction leading to male and female gametes (gametogony). As a result of fertilization, more than 100 millions of unsporulated, uninfective oocysts are formed and excreted in cat feces for up to three weeks. Sporogony takes place in the external environment 1-5 days after excretion of oocysts. Though oocysts are shed for only 1-3 weeks, even more than 100 millions may be shed [2]. They survive and remain infective for many months. Intermediate hosts ingest these infectious oocysts and enter into the asexual cycle [10]. Asexual cycle consists of two interconvertable stages; tachyzoites (acute infection) and bradyzoites (chronic infection). Oocysts rupture and release sporozoites that penetrate the intestinal epithelium and differentiate into tachyzoites. Tachyzoites replicate by endodyogeny, infect neighboring cells and disseminate throughout the body (brain, heart, lung, eye, muscles, placenta). In the presence of an adequate host immune response they are eliminated from the organism within a few weeks postinfection [5]. However, tachyzoites capable of escaping destruction differentiate into bradyzoites and form tissue cysts predominantly in the muscle and brain [10]. Less commonly cysts may appear in lung, liver, kidney and other visceral organs [5]. Intermediate hosts can also be infected by the consumption of tissue cysts through raw or undercooked meat. As a result, as soon as these tissue cysts are ingested by the next candidate susceptible host, liberated bradyzoites will invade the intestine of the new host and convert back to the tachyzoite form, thereby completing the asexual cycle [10,11].

Transmission

Intermediate hosts can be infected by several potential routes of transmission either vertical or horizontal (carnivorism). In this regard, infection may be acquired through ingestion of either tissue cysts (by consuming raw or undercooked meat) or infectious oocysts from environmental material (hands, water or food -unwashed raw vegetables- contaminated with feline faeces). Transmission can also occur via tachyzoites through organ transplantation, blood transfusion or even unpasteurized goat milk. Vertical transmission of T. gondii by tachyzoites from mother to fetus via placenta results to congenital toxoplasmosis. Definitive hosts acquire T. gondii by ingesting either infectious oocysts from environment samples or tissue cysts from intermediate hosts [12].

Congenital Toxoplasmosis

CnT results, almost exclusively from an acute, primary acquired maternal infection after conception. However, in rare instances, CnT is caused by either reactivation of latent infection in immune compromised mothers or reinfection with atypical strains of T. gondii [2,13.14].

The incidence and severity of disease depends on the gestational age of transmission. The rate of vertical transmission is higher in pregnants infected in late stages of gestation, ranging in the absence of specific therapy, from approximately <2% in the first 6 weeks of pregnancy to 90%, if mother is infected during the last weeks. The estimated average transmission rates per trimester of maternal seroconversion are 14% (1st trimester), 30% (2nd trimester), and 59% (3rd trimester) [2,12,15,16]. The overall risk of CT throughout gestation is 20-50% [15]. Contrary to vertical transmission rate, the severity of fetal disease is inversely related to the gestational age in which T. gondii was contracted. In early pregnancy, CT can cause chorioretinitis, blindness, hydrocephalus, intracranial calcifications, seizures, mental retardation, even miscarriage, stillbirth or neonatal death. However, if transmission occurs in late stages of gestation, infection is mild or subclinical. Although in vast majority of CnT, infected infants are asymptomatic at birth, symptoms may develop later in life (after weeks, months or years). Ocular disease, neurological deficiencies, mental retardation, epilepsy and deafness are common manifestations [12].

Treatment of the mother reduces the incidence of mother-to-child transmission but if fetal infection has occurred, it reduces the severity of clinical manifastations of CnT.

Interestingly, there is a wide spectrum of incidence of CnT globally. In the USA, the prevalence of congenital infection has been estimated by Guerina et al, to be one case per 10000 live births, rather than 1 per 1000 expected in view of previous studies [17]. Thus, out of 4 approximately million live births per year in the USA, 400-4000 infants with CnT are estimated to be born every year [18].

In France, the overall prevalence of CnT in 2007 was 3.3 per 10,000 live births and the incidence rate of the disease at birth was 2.9 per 10,000 live births; the estimated incidence rate of symptomatic congenital toxoplasmosis was 0.34 cases per 10,000 live births [19]. The prevalence of CnT observed in France in 2007 was in the same range as incidences reported in other European countries (Poland, Denmark and Switzerland) but much higher than that reported in Sweden19. According to a recent, systematic review the global annual incidence of CnT is 190100 cases, which amounts to an incidence rate of approximately 1.5 cases of CnT per 1000 live births [20].

Diagnosis of Congenital Toxoplasmosis

Diagnosis of CnT involves a. diagnosis of primary infection in a pregnant woman, b. demonstration of fetal infection prenatally and c. postnatal diagnosis in the newborn infant. It relies on serologic testing and parasite isolation by a combination of diagnostic tools (immunoassays, PCR approaches, Western–blott and mouse inoculation).

In pregnants, the mainstay of diagnosis of acute infection is antibody detection by serologic tests. Determination of immune serostatus of mother before conception is valuable, assisting in the interpretation of serologic results. The presence of IgG titers before conception in immunocompetent women is protective and provides life-long immunity. These women pose very little risk of transmission of infection to fetus. Nevertheless, rare cases of reinfection with atypical, more virulent strains may occur. Serological screening in all pregnants, ideally in 1st trimester, is warranted during gestation, in order to prevent CnT [21]. The Sabin-Feldman dye test, based on parasite lysis by serum antibodies in the presence of complement, is both sensitive and specific, and has been the gold standard of

diagnosis for many years [2]. Nevertheless, because of handling and working with live organisms, great caution should be taken in order to avoid contamination. Currently, the method has been replaced by newer techniques that are used as confirmatory tests in most reference laboratories [2], such as indirect fluorescence antibody tests (IFAT), immunoblot and immunosorbent agglutination assays (ISAGA) [1]. Enzyme-linked immunosorbent assay (ELISA) and chemiluminescence immunoassay (CLIA) consist automated screening methods used in clinical laboratories [1,2] .

Elevation of IgG titers in the absence of IgM indicates infection with T. gondii usually for more than 6 months, while seronegative pregnants are susceptible to infection and should be screened thoroughly during gestation, each month or trimester till delivery [15,21]. The absence of IgG and IgM antibodies though, may not rule out the acquisition of a very recent infection within the last 7 days, since IgM antibodies are produced the first week postinfection. If both IgG and IgM are positive, this implies either possible recent contamination within the last 12 months, or a false-positive IGM reaction. In such cases, the specificity of IgM detection should be confirmed by further testing in a reference laboratory [3,15]. Furthermore, IgG avidity may contribute to determine whether toxoplasma was first contracted after conception or not, provided the test is performed during the 1st trimester of gestation. In this instance, a high avidity ratio discards the possibility of an infection acquired in the preceding four months, regardless of IgM titers [2,21].

Once acute primary maternal infection during gestation is confirmed or even highly suspected the next step is to administer spiramycin to mother and determine fetal transmission ensuring appropriate prenatal counseling. It is well documented that immediate institution of treatment is associated with favorable outcomes. Fetal ultra sound examinations in conjuction with detection of *Toxoplasma gondii* DNA in amniotic fluid by PCR assays are performed in order to detect fetal infection. Amniocentesis should not be performed at less than 18 weeks' gestation and at least 4 weeks after suspected acute maternal infection because of false negative results [22].

Serodiagnosis of congenital toxoplasmosis in a newborn is complicated due to i) poor sensitivity of Toxoplasma detection that ranges from 25-60.9% [23,24,25] ii) the necessity to determine the origin of the detected specific anti-Toxoplasma antibodies and iii) lack of availability and cost of IgA detection kits [26]. IgG antibodies can cross the placental barrier, thereby complicating the interpretation of the serologic profile in the newborn. Discrimination between passively transmitted maternal antibodies and neosynthesized antibodies of newborn is of significant importance. However, increasing titers of IgG that persist more than 1 year indicate congenital infection, since maternal antibodies , though detected for several months, gradually decrease and usually disappear within 5- 8 months. However, treatment of infant with sulfadiazine and pyrimethamine, may suppress the synthesis of Toxoplasma-specific IgG antibodies, delaying the serological confirmation of the infection even up to the second year of life [27]. In contrast, both IgM and IgA specific antibodies cannot cross the placenta and their detection indicates CnT. However, their interpretation may be complicated due to placental leak reflecting contamination with maternal antibodies during labor [3]. Enzyme-linked immunofiltration assay (ELIFA) and Western Blott provide a comparative qualitative analysis of maternal and neonatal antibody patterns, in order to determine autonomous synthesis of antibodies in the serum of the neonate, particularly in newborns without T. gondii-specific IgM and/or IgA antibodies at birth [2,23,27].

Acquired Toxoplasmosis in Immunocompetent Hosts

Most cases (80-90%) of acute T. gondii infections in immunocompetent hosts are asymptomatic. In the remaining 10-20%, the course of the disease is benign and self-limited, with mild symptoms. The clinical manifestations include a mononucleosis-like syndrome, fever, cervical lemphadenopathy (discrete, usually non tender nodes from 0.5 to 3cm in diameter), asthenia and headaches. Non specific clinical signs and symptoms such as myalgias, pharyngitis, malaise, rash, or hepatosplenomegaly may also occur [2,5,28].

Extremely rare instances of severe disease in immunocompetent persons have been reported in the literature. Pneumonitis, myocarditis, meningoencephalitis, polymyositis and severe disseminated toxoplasmosis may be attributed to rare strains of T. gondii with atypical genotypes. It is well documented that the severity of the disease may depend on the genotype of the strain [2,29,30,31].

Diagnosis of Acquired Toxoplasmosis in Immunocompetent Hosts

Diagnosis of toxoplasmosis in immunocompetent individuals relies mostly on serologic testing and detection of different isotypes of Toxoplasma specific antibodies. Nevertheless, in the vast majority, diagnosis is not made at the time of seroconversion, because of mild or no symptoms. In rare occasions of severe disseminated disease direct parasite detection in blood and other body fluids may also be helpful through either parasite DNA isolation by real-time PCR, or through inoculation into mice or tissue culture cells.

Antibody Detection

The IgM-capture EIA eliminates potential interference by IGG and other isotypes exhibiting minimal nonspecific reactions [3]. Both IgM and IgA titers increase within first week following infection and fall after 1-6 months. However, in some occasions, IgM antibodies may be detectable for up to 18 months postinfection, whereas IgA declines a little earlier and disappears until 9 months. As a result, both IgA and IgM antibodies, though suggestive, cannot by themselves document recent infection and should not be used as a stand-alone test in order to differentiate acute from chronic infection. Detection of IgG isotype occurs within 1-3 weeks after the initial rise of IgM, peak in 8 weeks and subsequently decline but never completely disappear with residual titers of the immunoglobulin to remain life-long [2].

Absence of both IgG and IgM isotypes, excludes recent infection initiated more than 7 days ago. All IgM positive test results should be confirmed by a reference laboratory [3,15].

Ocular Toxoplasmosis

T. gondii disseminates into the retina via the bloodstream. Alternatively, parasites are directly spread into the optic nerve from an adjacent cerebral infection. Ocular toxoplasmosis is the commonest

cause of posterior uveitis globally and results from congenital or acquired infection. Whatever the route of contamination, lesions may develop during acute or latent stage of infection [32]. Interestingly, OT exhibits variable clinical signs and manifestations. The primary site of infection is retina, though the choroid, vitreous and anterior chamber of the eye may also be affected. White, focal necrotizing retinitis or retinochoroiditis, frequently satellite to a variably pigmented scar is the hallmark of OT. The scars consist the remnants of previous parasite attacks. Active lesions, either solitary or multiple, are typically accompanied by overlying vitritis which in the presence of severe vitreous inflammatory reaction may hide the details of the fundus, causing the classic "headlight in the fog" appearance. OT is often associated with granulomatosus or nongranulomatosus anterior uveitis and severe secondary iridocyclitis as well. Cataract, glaucoma, optic nerve atrophy, retinal detachment consist complications of OT. Active retinochoroidal lesion eventually converts into an atrophic retinochoroidal scar and recurrent episodes tend to occur mainly at the margins of old scars due to rupture of tissue cysts located within old lesions. As a result, feature of reactivations of congenital infection is the presence of an old retinochoroidal scar at the borders of which active lesion develops [33,34,35]. Atypical presentations and forms of OT include rhegmatogenous retinal detachment, serous retinal detachment, retinal branch artery or vein occlusion, punctate outer retinal toxoplasmosis, neuroretinitis, retinal or subretinal neovascularization [36].

A prompt and accurate diagnosis is crucial in order to direct immediate initiation of proper therapy and is generally clinical. It relies on thorough evaluation of typical opthalmologic features and signs. Subsequently, a favorable outcome following anti-Toxoplasma therapy confirms the diagnosis. Serological test results, though not conclusive, may offer aid in some occasions of either atypical ocular manifestations or inadequate response to specific treatment. Due to the high prevalence of seropositivity in the general population, the detection of circulating specific IgG antibodies is of low diagnostic value and does not establish diagnosis of OT [37]. On the other hand, undetectable IgG titers in the setting of immunocompetence, discards the possibility of Toxoplasma infection.

Analysis of intraocular fluids includes detection of local production of Toxoplasma specific antibodies (IgG and/or IgA) or identification of parasite DNA by PCR assays into aqueous humor and vitreous fluids. The sensitivity of PCR in ocular fluids ranges from 36% to 55%. Local production of Toxoplasma specific antibodies is measured by the Goldmann-Witmer coefficient (GWC) that compares the specific antibody profiles in the ocular compartment and in serum. Although a ratio of greater than 1 is abnormal and indicates intraocular synthesis, it may also been seen in healthy individuals. Values of at least 3 are considered significant and more supportive of diagnosis34. Alternatively, Western Blott can also reveal ocular production of specific antibodies. Undoubtfully, such approaches consist useful complementary diagnostic tools in order to narrow the differential diagnosis, particularly in complex cases, such as immunecomprimised or atypical cases but with strong clinical suspicion. However, ocular fluid extraction is an invasive procedure carrying risks for the patient [38].

In the majority of OT in immunocompetent patients, infection is self-limited and resolves spontaneously without any specific treatment. However, the institution of anti-Toxoplasma therapy is warranted i) in immunocompromised individuals, ii) in the presence of atypical manifestations, iii) in patients who have lesions located in key positions on the retina such as lesions that affect the macula or optic nerve or iv) have reached a critical size and in general terms, v) any sight-threatening lesion . Thus, several therapeutic regimens have been used. The most commonly used therapeutical scheme for OT, known as '"triple drug therapy" is the combination of pyrimethamine, sulfadiazine and corticosteroids. Folic acid supplementation is necessary in order to avoid hematologic complications caused by pyrimethamine, a drug regimen with several adverse reactions and side effects. The addition of steroids protects the retina from the inflammation. "Quadruple therapy" refers to the combination of pyrimethamine, sulfadiazine, clindamycin, and corticosteroids. Trimethoprim-sulfamethoxazole is administered as prophylactic treatment against recurrences of toxoplasmic retinochoroiditis. Nevertheless, several researchers propose trimethoprim-sulfamethoxazole as a new treatment option of a single agent treatment for active OT. Alternatively to oral therapy in OT, local treatment by the intravitreal injection of clindamycin plus dexamethasone has been proposed [34].

Toxoplasmosis in Immunocompromised

Unlike toxoplasmosis in immunocompetent subjects, in immunosuppressed (transplant recipients, patients with AIDS, systemic lupus erythymatosus (SLE), or immunosuppressive therapies), regardless of strains and genotypes, T. gondii accounts for opportunistic, potentially life-threatening infections, with unfavourable outcomes and poor prognosis. The immune status of the infected persons is crucial. It is well documented in the literature, that the intensity of immunosuppression alters the course of opportunistic infections. In most cases, severe disease is due to dormant cysts rupture and release of tachyzoites during reactivation of infection acquired in the distant past. However, in rare instances, toxoplasmosis results from recently acquired contamination by the parasite.

Risk groups: 1. Transplant recipients. Cerebral toxoplasmosis is considered to complicate solid organ transplantation and allogeneic hematopoietic stem cell transplantation (HSCT) [39].

In this cohort, severe or disseminated toxoplasmosis is a result of either transplantation of a cyst-containing organ of an infected donor into a seronegative recipient or reactivation of chronic infection to the recipient due to immunosuppressive treatment [2,12]. Diagnosis is often complicated due to nonspecific clinical manifestations and impairment of the recipients' immune response in view of immunosuppressive theparies or irradiation [40,41].

2. HIV-infected individuals. Toxoplasmosis is the leading cause of focal central nervous system disease in AIDS. High risk patients among HIV-infected subjects are those with CD4+ T-cell count below 100cells/μL or below 200cells/μL in the presence of opportunistic infection or malignancy [42].

3. SLE patients. Toxoplasmosis is a rare, under diagnosed complication of SLE. The disease may present as cerebritis or pericarditis, mimicking SLE manifestations that may result eventually

to wrong diagnosis, inappropriate treatment and fatal outcome. Noteworthy, clinical presentation of Toxoplasma encephalitis is nonspecific, compatible with CNS involvement in SLE, an entity known as neuropsychiatric lupus [43,44,45].

Cerebral Toxoplasmosis

Toxoplasma gondii has an affinity to the CNS (neurotropism), while the gray and white matter of the brain is the main target organ for parasite encystment. Nevertheless, other organs may also be affected, such as the lungs, retinas and the heart. Thus, toxoplasmosis may manifest as pneumonitis, retinochoroiditis and myocarditis as well [2,46]. Interestingly, infection may also occur secondarily due to the dissemination of parasites from the primary reactivation site [2]. CT consists life-threatening, necrotizing encephalitis causing multiple lesions, with a propensity towards the basal ganglia, corticomedullary junction, white matter and periventricular regions. Though, a solitary lesion may also be seen. The lesions represent abscesses with surrounding vasogenic edema and mass effect. Neuroimaging (CT and MRI) typically reveals multiple ring-enhancing lesions, sometimes with a eccentral focus of enhancement, termed "target sign". CT is fulminant and fatal if left untreated [4,5,42,47,48].

Prevalence rates of CT exhibit considerable geographical variation that depends on the incidence of T. gondii seropositivity in the general population [5]. Hopefully, since the introduction of highly active antiretroviral therapy (HAART) and prophylactic treatment with trimethoprim-sulfamethoxazole (effective against both Pneumocystis jiroveci and Toxoplasma infections) the incidence of CT has markedly fallen. Abgrall et al, by use of the French Hospital Database on HIV showed that the incidence of CT decreased from 3.9 cases per 100 person-years during pre-HAART era, to 1.0 cases per 100 person-years during the period after the availability of HAART [49]. The clinical presentation of CT depends on the number and localization of lesions and in most cases is subacute in onset of the disease. Symptoms are nonspecific, ranging from headache and fever that may progress to coma, if prompt treatment is not instituted. Hence, a wide variety of clinical manifestations have been documented such as seizures, altered mental status, visual disturbances, sensory loss, drowsiness, hemiparesis, ataxia, speech disturbances, confusion. CNS toxoplasmosis may also manifest as obstructive hydrocephalus in rare occasions [50].

Presumptive diagnosis of CT relies on clinical features, serological tests, molecular studies and neuroimaging findings. Clinical improvement and regression of lesions are expected following 2-3 weeks of specific therapy. Responsiveness to an empirical trial of pyrimethamine and sulfadiazine confirms the diagnosis of CT., whereas if the patient fails to respond or even deteriorates, an alternative diagnosis should be suggested and brain biopsy might be considered. Though direct identification of tachyzoites in biopsy samples makes a definitive diagnosis, brain biopsy carries risk of major complications, such as bleeding, damage to surrounding tissue and infection [42,51].

It is known that immunocompromised individuals fail to produce significant titers of specific antibodies. Toxoplasma seropositivity was absent in approximately 10% of HIV-patients with toxoplasmosis [52,53]. Furthermore, in late stages of disease, patients may convert to seronegative [42,54]. Thus, unlike immunocompetent subjects, in immune-compromised such as AIDS patients, a negative serology does not rule out the possibility of toxoplasmosis, especially in the presence of compatible clinical and radiological features. Furthermore, detection of IgG antibodies in serum cannot discriminate reactivation of chronic infection versus latency, unless rising titers of IgG antibodies are determined. As a result, increasing IgG levels may indicate the occurrence of a reactivated infection, in the presence of clinical symptoms [42].

Significant diagnostic aid is provided by contrast-enhanced MRI or CT of the brain. MRI is more sensitive and accurate than CT to detect lesions of CNS toxoplasmosis [4,50]. However, imaging features though characteristic, are not pathognomonic of the disease. Newer modalities, such as signal photon emission computed tomography (SPECT) or position emission tomography are useful in differentiating CNS lymphoma from CNS toxoplasmosis.42

The differential diagnosis of CNS toxoplasmosis in HIV infection includes primary central nervous system lymphoma, mycobacterial infection (tuberculous abscess, tuberculoma), fungal infection (cryptococcosis, aspergillosis), primary brain tumors (glioblastoma), brain metastasis, multifocal infarcts, progressive multifocal leukoencephalopathy, cytomegalovirus and herpetic encephalitis, bacterial brain abscess (Nocardia spp), trypanosomiasis, microsporidiasis, neurocysticercosis and neurosyphilis [5,42].

Conclusion

Toxoplasmosis emerges as a diagnostic challenge, as well as a major concern and worldwide problem of public health. Its clinical presentation ranges from an asymptomatic to a severe, deteriorating disease with potentially fatal outcome, depending on the immune status of the patient. In this context, prompt and accurate diagnosis is crucial and a requisite to guide effective management and prevent further complications.

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