TOXOPLASMA ENCEPHALITIS AFTER INITIATION OF HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY (HAART)

ENCEFALITE PÓS-TOXOPLASMA APÓS INICIAÇÃO DE TERAPIA ANTI-RETROVIRAL DE ALTA ATIVIDADE

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ABSTRACT

Since 1983, *Toxoplasma* encephalitis (TE) is the neurological disorder most frequently found in HIV/AIDS patients. It commonly develops as a reactivation, and its etiological agent is the obligatory intra-cellular protozoan *Toxoplasma gondii* (*T. gondii*). The parasite seropositive rate, which varies in different parts of the world but is significantly high in most of them, is what keeps concern about TE constantly present. The first antiretrovirals favored the same class and were used in single therapies; they were incapable of promoting sufficient immunological recovery to avoid opportunistic diseases and, furthermore, the concept of either primary or secondary prophylaxis had not been established at the time. In 1996 the appearance of two new antiretroviral classes triggered a new treatment concept. The existing prophylactic procedures were associated to a Highly Active Antiretroviral Therapy (HAART), a behavior that showed its efficacy in reducing the number of cases. *Toxoplasma* encephalitis has recently been described with an immune reconstruction inflammatory syndrome (IRS) related to the rapid response to HAART in severely immunodepressed individuals. Reports on reactivation or relapse noted in patients with sustained immunological recovery, when it is safe to suspend prophylaxis, suggest the participation of more aggressive *T. gondii* strains or factors inherent to the host. It is therefore necessary to carry out more wide-ranging studies to clarify the link between parasite/host and chronic/reactivated infections of cysts. Other alternatives to the treatment and prophylaxis of AIDS and TE that facilitate the adhesion of the patient to the first approach, as well as the definition of the serological *status* for *T. gondii* and the adoption of prophylactic measures related to primary infection cases, can largely contribute to reduce the number of TE cases.

Keywords: HIV, AIDS, *Toxoplasma* encephalitis, prophylaxis, immunological reconstitution, STD.

RESUMO

Neurotoxoplasmose (NT) é a afecção neurológica mais freqüente e a principal causa de lesões com efeito de massa em pacientes com AIDS. Desenvolve-se caracteristicamente como reativação de infecção prévia e seu agente etiológico é o protozoário intracelular obrigatório *Toxoplasma gondii (T. gondii).* A taxa de soropositividade ao parasita, diferente nas diversas partes do mundo, mas significativamente alta na maioria deles, mantém essa infecção como uma preocupação permanente. Os primeiros anti-retrovirais pertenciam a uma mesma classe e eram empregados em monoterapia, o que não promovia recuperação imunológica suficiente para evitar a instalação de doenças oportunistas. O conceito de profilaxia primária ou secundária também não estava estabelecido. A partir 1996, a existência de duas novas classes de medicamentos deu início à era do tratamento antiretroviral de alta atividade (HAART) que associado à profilaxia mostrou-se eficaz na redução do número de casos. Recentemente, a NT tem sido descrita como síndrome de reconstrução imune (SRI) e seu desenvolvimento está relacionado a baixas contagens de células T CD4+ associada à rapida recuperação da resposta imunológica obtida com os diversos esquemas HAART. Relatos de NT em indivíduos com reconstrução imune sustentada sugerem a participação de cepas de *T. gondii* mais agressivas ou fatores inerentes ao hospedeiro que precisam de maiores esclarecimentos. pois nem todos cronicamente infectados pelo parasita desenvolvem NT durante o período de doença avançada e há casos de evolução excepcionalmente grave.

Palavras-chave: HIV, AIDS, neurotoxoplasmose, profilaxia, reconstrução imunológica

INTRODUCTION

An infection caused by Human immunodeficiency virus type 1 (HIV-1) infection is associated with a large variety of neurological syndromes, that may compromise both central (CNS) and peripheral (PNS) nervous system. The etiologies can be infectious or not, and any segment of the CNS or PNS can be compromised. Immunological dysfunction resulting from HIV-1 infection triggers the vulnerability of the host to opportunistic diseases that define AIDS, and *Toxoplasma* encephalitis (TE) is the main and most frequent cause of the expansive lesions found in patients with AIDS among the causes that affect the CNS. The clinical type most commonly seen is encephalitis, that appears with fever and focal neurological signs that characteristically develop in advanced AIDS. The administration of primary prophylaxis is highly recommended for patients who present laboratory evidence of having suffered a prior infection by *Toxoplasma gondii* (*T. gondii*) in severely immunodepressed environments, due to its high morbidity, mortality and relapse incidence, and to administer secondary prophylaxis to those who develop TE, both of which are interrupted when a sustained immune recovery occcurs.[1,2]

New classes of antiretroviral drugs were approved after the establishment of the Highly Active Antiretroviral Therapy - HAART concept in 1996, such as the non-nucleoside analog reverse transcriptase inhibitor (NNRTI) drugs and protease inhibitors (PIs) that gave way to a new AIDS therapy concept. The administration of HAART increased survival time and reduced the number of opportunistic events, even TE. The immunological reconstitution provided by HAART also helped to reduce the time during which prophylactics were used, an important gain in the clinical handling of AIDS patients. However, medication interactions, intolerance, adverse effects – which result directly from the excessive quantity of medication necessary during the initial handling of the patient – make the adhesion to HAART or prophylaxis more difficult, and thus increase the risk of the patient developing TE. Several clinical trials are being carried

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out with other drugs, in order to find out how to reduce some of these problems[3].

The associated use of HAART and prophylaxis, and the parameters established for their interruption are also considered highly current and pertinent issues as, despite the proven efficacy of this behavior in reducing the number of cases, this is still considered the most prevalent CNS disorder.[4] Clinical manifestations are still observed in advanced HIV disease and, more recently, in the immune reconstruction system (IRS). Several studies are underway with *T. gondii* strains seeking to understand these phenomena better, and attempting to establish a link between chronic infection and cyst reactivation. Other aspects that must be taken into account are the existence of exceptionally severe evolution cases, reactivation of the disease in individuals who have attained a sustained immunological reconstruction through the administration of HAART, and the occurrence of TE in immunocompetent individuals that are not infected by HIV-1.

TOXOPLASMA GONDII

Described for the first time and almost simultaneously in 1908 by Splendore in Brazil and Nicole and Manceaux in Tunisia, *T. gondii* is an obligatory intracellular protozoan belonging to the *Apicomplexa* phylum. Its capacity to reactivate itself in the presence of immunossupression as encephalitis, was initially observed in transplanted patients or those with a malignant disease, but it was only after the emergence of AIDS that encephalitis took epidemic proportions. Capable of infecting and multiplying in virtually any mammalian or bird nucleated cells, the vital cycle of *T. gondii* is divided in the intestinal phase that occurs exclusively in phelideous whose main representative and defined host is the cat; and extra-intestinal, that can occur in the cat as well as in intermediary hosts. The parasite presents three infecting stages: tachyzoites, bradyzoites and sporozoites. The two phases of the parasite's vital cycle may occur simultaneously in the cat, but the only one that develops in the intermediate hosts is the asexual type. In man, after contamination has occurred, the bradyzoite divides rapidly in the intestinal cells and local lymphnodes, where it transform into a tachyzoite that rapidly disseminates through the blood and lymphatic circulations and can virtually reach any organ. There is intense formation of new tachyzoites in the invaded cells that characterize their proliferation phase. The cells are destroyed by lyse, and free the infectants that invade the new cells. The average duration of this process is two or three weeks in immunocompetent individuals, and is related to the severe phase of the disease. The severity of the clinical history of the dissemination phase depends on the quantity of infected types acquired, the strain of the parasite as well as the susceptibility of the host. In fetuses and immunocompromised individuals, the evolution may follow a fatal course. The specific antibodies (Ab) that appear destroy the extra-cellular forms, and reduce the reproduction speed. The resistant tachyzoites are isolated from the organism through the formation of cysts located in the cellular interior, where they return to the bradizoyte form, with low multiplying power. These cysts remain latent and feasible for the rest of their lives and are more commonly located in the nervous system, retina and skeletal and heart muscles. A necrotic focus is created in the place that housed the destroyed cells, inducing an intense inflammatory response. The occurrence of a failure in the immune mechanisms, allows the bradyzoites contained in the cysts to return to a rapid proliferation form (tachyzoites), re-starting a new parasitemia.[5]

An interesting characteristic of the tachyzoites external membrane is that all of its proteins are anchored through glycophosphatidilinositol (GPA) bridges and p30 (or SAG1), the most abundant one, is one of the antigenes (Ag) recognized in the human serum. On account of their high immunological power they induce the production of IgG, IgM and IgA, and the two latter are he ones that underline a severe infection diagnosis. Another protein, p22 (or SAG2), is less immunogenic and stimulates the production of IgG, but has little capacity to induce IgA and IgM responses and can be used as a marker for chronic infection.[6]

GENETIC AND VIRULENT CHARACTERISTICS OF STRAINS

Several studies have been carried out since the last century on the existing link between the virulence of a strain and the development of a disease in human beings[7]. More and more research is being done to clarify the relationship this parasite establishes with the immune system of the infected individual, as well as to develop vaccines and propose new diagnostic therapy approaches and methods, all of them triggered by global publicity on issues related to the HIV-1 virus. The immunodeficiency arising from this infection increased the incidence of cases of toxoplasmosis-disease changed its common clinical presentation, fostering further research to enhance the understanding of the behavior of this parasite. Different methods can be used to characterize the parasite, such as: isoenzymes electrophoresis, restrictor fragment polymorphism/RFLP or DNA analysis (*Deoxyribonucleic acid/DNA*). Three groups of enzymatic standards with different degrees of virulence were described, and three clonal *T. gondii* lineages were later classified as virulent, non-virulent and with intermediary virulence. However, due to the controversial findings obtained to date, it is impossible to establish the relation between strains and the severity of the clinical expression of the infection.[7] Other analyses must be carried out using a larger number of samples, in order to clarify the influence of the different *T. gondii* strains on human infection, especially in patients with AIDS.[8] It has been suggested that the participation of "wild" genotypes or the acquisition of a new isoenzyme by the parasite, may explain the existence of severe clinical forms in immunocompetent adults with primary infection or the reactivation of the disease in individuals infected by HIV-1 and the immunological reconstruction obtained with the administration of HAART.[9] The degree of virulence of the strains has no well-defined molecular or immunological classification yet, and the main assessment criteria used is the percentage of animals that do not survive the experimental infection and the survival time of those who fail to resist it.

IMMUNE RESPONSE TO INVASION

Parasitic infections are characterized by a large quantity of Ag, host specificity and chronicicity. Countless immunological defense mechanisms such as the inborn, humoral and cellular

immune response (IR) are necessary to obtain an efficient IR, noted in patients with laboratory evidence of having been previously infected by *T. gondii*, who do not develop the clinical disease. The different functions of the population of T – $CD4^+$ e $CD8^+$ – lymphocytes are at times superimposed, such as the T $CD4^+$ lymphocyte, considered more important due to the regulatory role it plays on the functioning of the remaining cells of the immune response (IR): other T lymphocytes, B cells, macrophages and natural killer cells/NK. The T $CD4^+$ cells bind to the class II Major Histocompatibility Complex/MHC of the cells that present the Ag and T $CD8^+$ than bind to the MHC class I molecules. The T helper $CD4^+$ lymphocytes are subdivided into Th1 and Th2. The T $CD4^+$ Th1 response plays a protective role by producing mostly interleukin 2 (IL-2), interferon gamma (IFNγ), a tumoral alpha and beta necrosis (TNFα and TNFβ) and interleukins Th2 4, 5, 6, 10 and 13, among which IL-4 and IL-10 are the most important. The T $CD8^+$ lymphocytes also participate in the process of destroying the parasites, through the cytotoxicity of the infected macrophages and the production of IFNγ. The humoral and cellular IR interact throughout the severe infection in order to control it: an activation of the macrophages occurs as well as the production of IFNγ and the stimulation of the T $CD8^+$ lymphocytes, considered the most important cells directly responsible for the defense against *T. gondii*, while the T $CD4^+$ plays a synergistic role.[10]

As the main HIV-1 target, the T CD4+ cells account for the balance drawn between the Th1 and Th2 response. In view of the fact that the predominant subpopulation determines the result of the infection, Th1 plays an essential role in the response to *T. gondii*. In individuals with HIV/AIDS, the progressive loss of T CD4+ lymphocytes breaks the balance of the Th1 and Th2 response, facilitating the multiplication of the parasites. This is why the clinical disease is most commonly found during the advanced phases of immunodepression, when the balance of these responses is quite significative. *Toxoplasma gondii* stimulates the production of Ab of IgM, IgG, IgA and IgE classes, and is a powerful inductor of the Th1 type response, essential to ensure the growth control of the parasite. One of the causes of reactivation of tissue cysts in immunodeficient individuals, especially those with AIDS, could be attributed to failure to produce IFNγ and IL-2. All mechanisms are not fully explained and it is quite possible that other factors also contribute to cause the reactivation, such as the HIV-*T. gondii* co-infection, the genetic factors of the host and/or infection caused by a more aggressive strain[8].

The behavior of an organism acutely infected by *T. gondii* shows some intriguing aspects. Although the infection unleashes an intensive, constant cellular IR through specific and non-specific mechanisms, in immunocompetent individuals this reaction is normally discrete[11]. Low titers and the constant liberation of Ab seem to account for the resistance to reinfection. IgA is an important element for mucus immunity and plays a protective role when faced with an oral contamination risk. The infection becomes chronic and asymptomatic due to the fact that the walls of cysts containing the surviving bradyzoites are formed by elements resulting from the host. This characteristic protects the parasite against the immune system and its feasibility throughout the life of the chronically infected individual. The molecular mechanisms that allow this type of response modulation, will solve the enigma related to the successful co-existence established between human hosts and the parasites, hidden in AIDS, where the intensification of the infecting forms are noted together with the new parasitemia. In the CNS, one the favorite locations of the cystic parasite, the loss of IR control leads to the development of NT.

PREVALENCE, TRANSMISSION FORMS AND PREVENTIONMEASURES

Toxoplasmosis is a globally distributed zoonosis with variable prevalence rates in different parts of the world. It is estimated that in tropical countries approximately 90% of the population show laboratory proof of having been previously infected. In the rest of the world, these rates vary between 50% and 60%. These percentages may be affected by the climate, geographic characteristics or transmission modes. The seropositive rate increases with age. An epidemiological study carried out in Brazil showed a positive prevalence for toxoplasmosis in 80% of the adult population[12].

Human infection occurs through contact with a protozoal in different forms (bradyzoite, tachyzoites, sporulated oocyst containing sporozoite or cysts containing bradyzoite) and through different ways of transmission: congenital, organ transplants, parenteral; occupational infection is rare and oral infection occurs more frequently[5]. Pregnant women and seronegative individuals for infection caused by *T. gondii*, as well as fetuses and immunodepressed individuals are more susceptible to infections. Prophylactic measures include not feeding raw or barely cooked meat to domestic cats; keeping animals inside the house in order to prevent them from hunting rats and birds; avoiding direct contact with cat feces; changing the sand in the litter box every day and avoid contact with those found in public places; washing one's hands after touching the soil or an animal; avoid consuming or badly cooked meat, non-pasteurized milk and water of unknown origin; combating mechanical vectors such as cockroaches and flies; basic sanitation.

Researchers from the Tropical Medicine Institute in São Paulo and the Molecular Biology Laboratory of the Energy and Nuclear Research Institute (IPEN) have recently developed what might become the first anti-*T. gondii* vaccine. This vaccine is based on the ionizing radiation principle. After purification, the tachyzoites are exposed to a cobalt-60 source. The doses are not lethal, but sufficient to alter its reproductive capacity, keeping the organism viable. Initial tests were carried out with mice, through an oral administration, and obtained a significant reduction of tissue lesions without registering any deaths among the test animals. The initial results were promissing.[13]

DIAGNOSIS

The diagnosis can be indirect, using serologic methods, or direct through a Polymerase Chain Reaction/PCR, hybridization, isolation or biopsy. Several biological materials, such as peripheral blood, amniotic liquid fluid, cerebrospinal fluid (CSF) or urine may be used to visualize the parasite. The most common diagnos-

tic method used in clinical practice in Brazil is the specific Ab serology against *T. gondii* Ag. IgM and IgG can be detected by indirect immunofluorescence (IIF), hemoglutination and immunoenzimatic tests, that are the most commonly used, such as ELISA (*enzyme-linked immunosorbent assay/Elisa*). Culture, isolation of the parasite or PCR (polymerase chain reaction) involve high costs and are only indicated in exceptional situations.

Acute infection is diagnosed by the presence of Ab of the IgM class that appears in the serum four to five days after infection, and IgG after two to three weeks. Dosages for low IgM titres remain manageable for up to one year. While those of IgG increase up to the maximun value in six to eight weeks, dropping slowly to basal levels for the remaining life span. The presence of IgG and IgM can occur simultaneously, depending on the collection phase of the material. These laboratory characteristics hinder the interpretation of the results, which becomes more difficult.

Whenever that doubt exists, the IgG avidity test can point out the difference between acute and chronic infection. At the onset of the infection, IgG shows low avidity by for the *T. gondii* Ag, while in older infections the avidity was high. Low avidity indexes are lower than 30%, because they show that the infection occurred over the last 4 months. Indexes above 60% are considered high, and indicate that the infection occurred more than 4 months ago. Values between 30% and 60% do not permit the disease phase to be determined. Another resource available is the study of IgA in saliva or serum, as an acute infection marker. AIDS and TE patients may present unsatisfactory results when using this material.[14] The IgG elevation without an increase of IgM suggests the presence of an infection, but that it is not acute.

As in AIDS patients TE is related to the reactivation of a prior infection, the interpretation of the serology results may be quite problematic. The simple presence of IgG does not determine a reactivation diagnosis. During the exacerbation of severe immunodeficiency, the increase of IgG or IgM values may go unnoticed. IgG results in a latent infection diagnosis and only 3-6% of patients with AIDS and TE show negative serology. It is extremely important to know the serologic anti-*T. gondii* profile of these patients as soon as the HIV-1 infection diagnosis is confirmed. In individuals with clinic reactivation suspicion the seric anti-*T. gondii* antibodies show a positive predictive value above 80%.[15] The CSF research is not specific because the Ab may only represent passive transfer through the blood-brain barrier.

A presumptive diagnosis of CNS toxoplasmosis is based on clinical symptoms, serologic evidence of *Toxoplasma*-specific IgG, presence of a space-occupying lesion on imaging studies of the brain, and objective response, on the basis of clinical and radiographic improvement, to specific anti-*T. gondii* therapy in the absence of a likely alternative diagnosis.[1]

Computed tomography (CT) scan reveals multiple, bilateral, hypodense, contrast-enhancing focal brain lesions. Contrast enhancement often creates a ringlike pattern surrounding the lesion (**Figure 1**).

Magnetic resonance imaging (MRI) is more sensitive than CT scan and often shows evidence of multiple lesions. These lesions frequently involve the basal ganglia, hemispheric corticomedullary junction and brainstem (**Figure 2**). These findings are not pathognomonic, because 40% of the lymphomas are multifocal and 50% capture contrast with an annular or nodular reinforcement images similar to those of TE.[16] An example of this similarity can be seen in Figure 3. There is a 10% false-negative result obtained with both neuroimaging methods. The presence of a single lesion increases the primary lymphoma diagnosis four-fold, and a brain biopsy may be necessary. Despite the new radiological methods, the difficulty in distinguishing TE from a primary lymphoma is still a widely discussed subject.

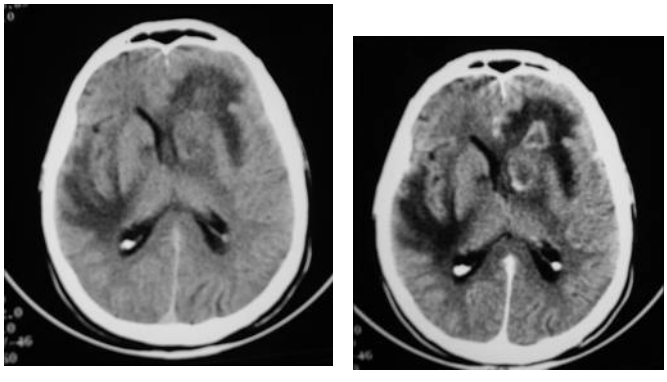

Figure 1. Brain CT of patient with AIDS and TE.
(A) without contrast administration and (B) with contrast administration

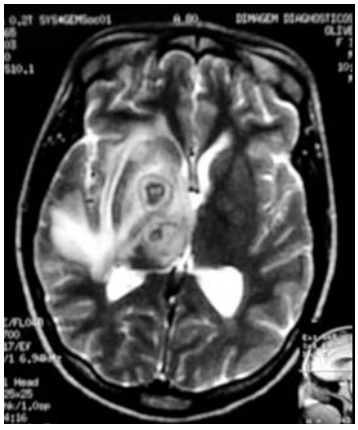

Figure 2. Brain RM of patient with AIDS and TE.

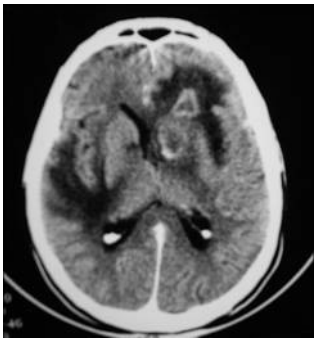

Figure 3. Brain TC of patient with AIDS and primary brain lymphoma

Definitive diagnosis of TE requires histologic or cytologic confirmation by brain biopsy, which might demonstrate leptomeningeal inflammation, microglial nodules, gliosis, and *Toxoplasma* cysts. Biopsy should be considered when early neurologic deterioration is present despite empiric treatment fail to respond to anti-*Toxoplasma* therapy after 10-14 days.

CLINICAL FINDINGS

An infection by *T. gondii* proves the presence of viable microorganisms in an individual. From a clinical standpoint, toxoplasmosis is a sign of infection, and indicates an active morbid process that is rarely present. It is characterized by two stages: acute (recently acquired or first infection) and chronic (-latent). In immunocompetents, including adults, pregnant women and children, the acute form is oligosymptomatic, self-limited, goes unnoticed or exists with cervical, occipital or submandibular lymphadenopathy, fever, myalgia, probable exanthema, and rarely needs a specific treatment. On the other hand, ocular toxoplasmosis, persistent intermittent lymphadenopathy, widely spread severe evolution or a similar form of mononucleosis occur less frequently. Myocarditis, polymyositis, pneumonites, disseminated forms of septic shocks in general are associated with immunodeficiency.[17] The behavior of the parasite changes when an infection attacks a fetus or in the presence of immunity disturbances. Individuals using immunosuppressive drugs, transplant receptors or those with AIDS present more aggressive forms.[17] Congenital toxoplasmosis occurs when a woman acquires *T. gondii* during pregnancy, because tachyzoites break through the placenta barrier reaching the conceptus cells. Very rarely, the conceptus may be affected by the reactivation of a chronic disease in pregnant women in an advanced stage of AIDS.[18] Clinical characteristics observed in the neonate are directly related to the intra-uterus development phase where the infection occurred, that is much worse during the first trimester when it can still cause a spontaneous abortion.

Currently, the most common cause of immunodeficiency is the one that results from HIV-1 infection. In these patients, cyst reactivation usually occurs in the CNS, and causes TE. The acute infection with neurological manifestations is extremely rare, and very few cases have been described in the literature. The clinical manifestations of TE vary and include signs and symptoms of focal or generalized neurological dysfunctions or, more commonly, an association between both forms, depending on the number, size and location of the cysts. Brain edema, vasculitis and hemorrhage, which can also occur simultaneous with an active infection, also contribute to the pathological process. The signs and symptoms may appear in an acute or subacute form and rarely follow a sudden course. The most frequent clinical aspects are those which involve focal neurological signs directly correlated to the anatomic location of the lesions, and hemiparesis is the one most commonly encountered. Other common findings are: headache, seizure and disturbance of consciousness.[19] Furthermore, hemianesthesia, brainstem syndrome, cerebellar syndrome, movement disorders and neuropsychiatric or psychological alterations may also be observed. In addition to these characteristics, some patients may develop a diffuse form of TE called "encephalitic", with multiple microabscesses and sensory disturbance with minimal focal signs. As TE is predominantly intra-axial, a significant meningeal compromise is not usually frequent, and explains the rarity of signs and meningeal irrigation symptoms. Chart 1 describes the clinical outlook of TE.

CHART 1. Neurological dysfunctions of the encephalic form of toxoplasmosis in patients with AIDS

Cerebral, cerebellar and brainstem dysfunctions	**Generalized cerebral dysfunctions**	**Neuropsychiatric dysfunctions**	**Other findings**
Hemiparesis, hemiplegia	Lethargy	Dementia	Pan-hypopituitarism
dysphasia, aphasia	Confusion	Anxiety	Diabetes insipidus
Hemianesthesia	Comma	Personality changes	Syndrome of inappropriate antidiuretic hormone
Seizures	Cognitive impairment similar to the AIDS dementia complex:	Psychosis	Hydrocephalus
Ataxia	- Decreased recent memory		Severe and localized headache
Cerebellar tremors	- Decreased attention		Untreatable
Movement disorders	- Slowed verbal responses		Hiccups
Parkinson syndrome	- Slowed of motor responses		
Cranial nerve palsies			
Visual field deficits			
Thalamic syndrome			

OTHER PRESENTATION FORMS

Meningoencephalic	**Similar to metabolic encephalopathia**	**Acute onset, encephalic**
Seizures, confusional state, meningeal irritation, comma. Suggestive signs of metabolic encephalopathia	Mioclonus & asterixis	Acute disseminated infection, rash similar to rickettsias, encephalitis, miocarditis and polymyosite, without focal signs and without CT or MRI imaging.

A primary infection or reactivation of cysts located in the CNS is rarely found in individuals with no previous signs of immunodepression.[20] Despite the high frequency of the encephalitic form, toxoplasmic myilitis is rarely reported. The causes that might justify them are unknown because the intramedullary form is not seen very often. The spinal cord disorder has no preferred location (cervical, thoracic or lumbosacral), and results in signs and symptoms related to the different levels of the lesion. Most patients show constitutional manifestations (fever, asthenia) and advanced infections through HIV.[21] In the post-HAART era, TE has been considered an IRS that develops days to months after the initiation of HAART.[22] The recovery of the capacity to produce immune responses that results from the antiretroviral therapy, and causes the development of a paradoxal inflammatory reaction against a latent or subclinical condition that may or may not be of an infectious nature. Low T $CD4^+$ counts and a powerful immune response are risk factors hindering the development of IRS. Usually, the evolution in most cases is favorable because the outstanding inflammatory reaction could imply an excellent response to HAART in terms of an immunological recovery. Nevertheless, in some cases it might result in a severe turn when the HAART scheme will have to be interrupted.

TREATMENT, PRIMARY AND SECONDARY PROPHYLAXIS

The main goal of therapy is to destroy the forms of parasitic tachyzoites. The bradyzoites located inside the cysts are resistant to all drugs used to date, and are therefore responsible for the chronicity of the infection. The treatment chosen for TE is the association of sulfadiazine with pyrimethamine, during an average of three to six weeks. Folinic Acid should be administered due to the effects of the pyrimethamine antifolate. A longer therapy period may be needed in severe cases or when there is no clinical and/or radiological solution. For those who are allergic or do not tolerate sulfa, clindamicin can substitute sulfadiazine, and should be prescribed associated with pyrimethamine.[1] There are several other therapeutic regimes currently that can be suggested to substitute the sulfadiazine/pyrimethamine and clindamicin/pyrimethamine programs (C+P). The association of SMX+TMP is presently being used to substitute the first choice, obtaining equivalent results.[23]

Other drug combinations proposed showed similar results. The effect of macrolides such as: azithromycin, clarithromycin, roxithromycin and spiramycin, was assessed in association with pyrimethamine, as an alternative choice to the usual treatment, but no improvement was noted with regard to its efficiency, and the doses administered are still considered controversial.[3] Spiramycin is a drug that has been suggested to treat pregnant women because it is less toxic, but its isolated use is not efficient in TE. Atovaquone is another drug for those who do not tolerate sulfa or do not respond to the programs previously mentioned. Although it is not very toxic for human cells, its driving mechanism is still unclear. It is more commonly used in pneumocystosis. In TE cases it was administered isolatedly or in association with pyrimethamine, sulfadiazine or azithromycin. Other suggested treatments are: 5-fluorouracil + clindamicin, doxiciclyn + pyrimethamine, clarithromycin + minocycline, trimetrexate, and dapsone isolated or in association with pyrimethamine. Rifabutin proved to be active in murines and was tested in animals in combination with other drugs. None of these regimes was universally accepted as an efficient alternative. Immunotherapy was also suggested as an alternative to these drugs, after reaching a breakthrough in the knowledge of the molecular biology of the parasite. Several studies are being carried out examining the different uses for IL-2, IL-6, IL-12, IFNγ and TNFα, in order to eradicate the parasite cystic form found in the organism, modifying the chronic nature of the infection. This is still at an experimental stage, and preliminary results show its efficiency is doubtful. The use of associated corticotherapy should be reserved for transtentorial herniation risk cases, due to the intensity of the brain edema. Its use may hinder the interpretation of the response to an empirical therapy, due to the clinical and radiological improvement achieved. Corticosteroids should therefore only be used when the intracranial pressure increases, because they can have no influence on the clinical response or survival.[24]

The implementation of primary prophylaxis is indicated for individuals with IgG^+ anti- *T. gondii* and a T CD4+ < 100-200 cells/mm^3 cell count. The secondary prophylaxis, on the other hand, is indicated for those who developed TE. The primary should be continued until the T $CD4^+$ cell values reach a value of > 200 cells/mm^3 sustained for ≥ 3 months, and the secondary will start right after suspension of the treatment, when the T $CD4^+$ cell count reaches > 200 cells/mm^3, sustained for ≥ 6 months. The procedure will restart if parameters are lost; this happens when errors in the antiretroviral therapy occur.[2] Prophylactic treatment, whether primary or secondary, should be preferably administered jointly with sulfadiazine + pyrimethamine, SMX+TMP, dapsone + pyrimethamine and atovaquone associations, with or without pyrimethamine. The isolated use of dapsone, pyrimethamine, azithromycin or clarithromycin is not indicated due to lack of available data about its efficacy.[1]

The criteria adopted for primary and secondary prophylaxis were established by the Centers for Disease Control and Prevention (CDC), but have been modified throughout the HAART era, as a consequence of a large number of papers published on this issue. Nevertheless, CDCs has some restrictions because despite the volume of existing publications, the number of cases studied is still considered too low to issue final recommendations. Another issue is that none of the published papers have examined the interruption of prophylaxis, whether primary or secondary, specifically for TE. It has always been analyzed within the context of other opportunistic infections, especially pneumocystosis, and included different treatment schemes, thus making it impossible to reach a consensus. With reference to TE, the primary prophylaxis item is currently no longer presented separately. All to the contrary, it is included in parallel with the benefits provided by HAART. There is only one restriction, that refers to the fact that the reactivation risk is greater in individuals with T $CD4^+$ < 50 cells/ mm^3 cell values and rare in those with T $CD4^+$ > 200 cells/mm^3.[1]

CONCLUSION

Toxoplasma encephalitis (TE) is a typical disease of advanced AIDS, and the introduction of prophylaxis when used associated to HAART significantly reduced the number of cases. Despite the efficiency of this approach, TE is still the prevailing CNS disorder. Although advanced immunodeficiency is its main inherent factor, in the post-HAART era TE has been described as an Immune Reconstruction Syndrome (IRS) or as a reactivation or relapse in individuals presenting consensual immunological defenses considered safe, if prophylaxis is interrupted. Additionally, some cases showing an exceptionally severe evolution, and those noted in immunocompetent patients, suggest the participation of more aggressive strains of *T. gondii,* or factors inherent to the host. Thus more detailed studies of the *T. gondii* strains and immune system behavior after entering in contact with this protozoan are required, in order to assist us to understand the relationship that exists between the parasite/host, and the chronic infection/cyst reactivation. New alternatives for AIDS and TE therapy and prophylaxis, that would facilitate the adhesion of the patient right from the start, the definition of the serological *status* for *T. gondii,* and the adoption of prophylactic measures related to the first infection, may contribute to the reduce the number of TE cases.

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Recebido em: 11/06/2008

Aprovado em: 22/07/2008