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Editorial

Is Toxoplasmosis A Neuroinflammatory Disease?

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Toxoplasmosis is the most frequent parasitic disease in the world, developing asymptomatically in the majority of cases in immunocompetent patients. However, in immunocompromised patients, toxoplasmosis develops more severely, with relevance for manifestations in the central nervous system [1]. This parasitic infection is caused by *Toxoplasma gondii*; an apicomplexa protozoan that belong to Supergroup Chromalveolata [2,3]. It is estimated that 30 - 70% of the human population is infected with this protozoan [4], an obligate intracellular parasite, that can infect most nucleated cell types in all warm-blooded species, being considered one of the most extraordinary parasites of all time. This protozoan has a fantastic machinery that facilitates its invasion, which occurs through active displacements of itself and the extrusion of its conoid, a highly dynamic cytoskeletal structure located at its extremity, sits within the apical polar ring [5] where the recognition of the cellular ligands is made, initiating the process of cellular invasion [6]. In addition, this structure allows sequential secretion of proteins contained in other organelles, such as micronemes and rhoptries; which are involved in creating the moving junction that allows the entry the parasite in the cell and in building the parasitophorous vacuole in which the parasite will develop [7].

As previously mentioned *T. gondii* infection in immunocompetent individuals is generally subclinical or associated with nonspecific symptoms. However, toxoplasmic encephalitis has become one of the most frequent opportunistic infections in immunocompromised patients; causing severe brain injury, coma and death [8]. In HIV / AIDS patients, *T. gondii* infections in the Nervous System (NS) can lead to necrotizing lesions in the basal nuclei, affecting the dorsal striatum (caudate nucleus and putamen), globus pallidus, ventral striatum (nucleus accumbens and olfactory tubercle) ventral pallidum, substantia nigra, and subthalamic nucleus; structures responsible by motor functions [9]. Patients immunocompromised by other etiologies or in treatment with cytotoxic drugs and glucocorticosteroids may also develop neurological complications [10,11]; as well as depression, anxiety and schizophrenia episodes [12].

Going against what was previously thought, *T. gondii* presents a differential preference invasive and development in neuronal cells in relation to the course of infection; it was believed that predominantly, the parasite exhibited tropism by glial cells. However, the parasite has an ability to infect a larger number of glial cells only in the acute phase of infection [13,14]. The interconversion phase occurs predominantly in neuronal cells, resulting in bradyzoite-filled cyst development [15,16]. This fact, possibly representing an adaptation along the evolution between *T. gondii* and its hosts; demonstrating the ability of *T. gondii* to manipulate the behavior of hosts in relation to predator-prey interactions [17,18]. Thus, bradyzoites have the ability to produce a protein homologous to tyrosine hydroxylase, an enzyme important for the process of dopamine synthesis, releasing it into the cytoplasmic space of infected cells [19]. It is possible that changes in the concentration of dopamine produced by *T. gondii* will interfere with the functions of locomotion, cognition, memory, learning and reward, directly interfering the behavior of the intermediate host favoring the parasite [20]. Preliminary studies, conducted by our group, found behavioral variations between mice infected with clonal strains versus field isolates of *T. gondii*, regarding motor activity, learning, evocation and extinction of aversive memory, with concomitant anxiety evaluation (Andrade J.M.A 2016, unpublished data).

It is known that *T. gondii* is able to immunomodulate its host for the success of the infection. The parasite simultaneously stimulates the secretion of protective cytokines (IFN-γ and IL-12) and paradoxically inhibits this response [21]. This double capacity of the parasite is beneficial and allows a stable parasite-host interaction to be established. Failures in the balance of this immune response have negative consequences for both [22]. *T. gondii* can also evade the immune response by acting on the host chromatin structure and inhibiting the binding of transcription factors to the promoter of the cytokine genes, as observed in a TNF-α study [23].

The parasite apparently has the ability to determine its own fate, maximizing its persistence and minimizing host immunopathology by inducing cytokines with anti-inflammatory properties such as TGF-β, IL-27 and IL-10. This latter cytokine is highly immunoregulatory during *T. gondii* infection [24] and it is often produced concomitantly with IFN-γ and IL-17, preventing tissue destruction by balancing the Th1 / Th2 responses [25]. The Th17 cells, producing IL-17, play a crucial role in the induction of autoimmune tissue injury. IL-17 can induce the rupture of the endothelial junctions that form the blood-brain barrier and, consequently, the Th17 lymphocytes can cross the vascular endothelium and destroy neurons, promoting inflammation in the central NS [26]. However, the cytokine IL-27, which is constitutively expressed in the retinal ganglion and photoreceptor cells, in response to IFN-ã may reduce the duration of the immune response, acting as a potent inhibitor of the development of Th17 cells.

Studies suggest that chronic infection of *T. gondii* may be the infectious agent for the development of various neurodegenerative diseases associated with an increase of several pro and anti-inflammatory cytokines, including IL-1b [27,28]. The importance of inflammatory mediators in the pathophysiology of brain disorders has been documented for schizophrenia, major depression, brain injury [29] and bipolar disorder [30]. A similar event may occur with some more pathogenic *T. gondii* genotypes; activated microglia, could significantly induce production of a large array of inflammatory cytokines and mediators such as IFN-γ, TNF, NO, IL-1 and IL-6 commonly present during toxoplasmic encephalitis affecting neurotransmitters [29]. In addition to the parasite lineage, the host genotype may influence the morbidity of the disease. Polymorphism in regulatory regions of cytokine genes as well as Toll-like receptors (TLRs) play a key role in regulating the type and magnitude of the immune response, and thus the polymorphic nature of these genes may confer greater flexibility on the immune response [31]. In this sense, immunogenetic studies conducted by our group showed an association between neuroretin lesion development and the presence of polymorphic or heterozygous alleles for the APEX-1 gene in human patients; associated with NF-kB that is involved in cytokine synthesis and drive for a protective immune response (Aloise D.A. 2016, Unpublished data). In seeking to understand these interactions associated with immune response and brain disorder, currently, we are conducting assays to evaluate changes in mouse brain connectivity and synaptic communication with chronic toxoplasmosis, noting the effect of neuroinflammation on the perineuronal networks.

Toxoplasmosis is a parasitic disease that remains profoundly under studied and underfunded in relation to the severity of the disease, with consequences still unknown to some clinical manifestations. Thus, investments are needed to improve the prevention, diagnosis and treatment of this disease. To control toxoplasmosis, a combination of antifolates, such as pyrimethamine and sulfadiazine, have been used and are the first choice drugs in most clinical settings [32], however these drugs have several adverse and toxic effects [33]. This therapeutic limitation raises a great concern, once, that in a recent study carried out by our research group, showed that *T. gondii* isolates obtained from farm animals used for human consumption presented resistance to treatment with sulfadiazine [34]. These data are of great importance, since sulfadiazine is the reference drug in the treatment of toxoplasmosis [35]. Thus, these strains may be involved in clinical complications and therapeutic failures observed in Rio Grande do Norte State / Brazil [34,36]. Other authors have reported the possible relationship between resistant parasites and therapeutic failures in 10% of cases of cerebral toxoplasmosis in patients treated with sulfadiazine [37].

Considering the broad adaptability of *T. gondii* to its hosts, as well as its ability to immunomodulate, studies are needed to better understand the parasite-host interaction of this incredible protozoan.

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Bibliography

1. Furtado JM., *et al*. "Toxoplasmosis: a global threat". *Journal of Global Infectious Diseases* 3.3 (2011): 281-284.

2. Adl SM., *et al*. "The new higher level classification of eukaryotes with emphasis on the taxonomy of protists". *Journal of Eukaryotic Microbiology* 52.5 (2005): 399-451.

3. Adl S M., *et al*. "The revised classification of eukaryotes". Journal of Eukaryotic Microbiology 59.5 (2012): 429-493.

4. Boothroyd JC and Grigg M E. "Population biology of Toxoplasma gondii and its relevance to human infection: do different strains cause different disease?" *Current Opinion in Microbiology* 5.4 (2002): 438-442.

5. Morrissette NS and Sibley L D. "Cytoskeleton of apicomplexan parasites". *Microbiology and Molecular Biology Reviews* 66.1 (2002): 21-38.

6. Carruthers VB and Sibley L D. "Sequential protein secretion from three distinct organelles of Toxoplasma gondii accompanies invasion of human fibroblasts". *European Journal of Cell Biology* 73.2 (1997): 114-123.

7. Dubremetz J F. "Rhoptries are major players in Toxoplasma gondii invasion and host cell interaction". *Cellular Microbiology* 9.4 (2007): 841-848.

8. Osunkalu VO., *et al*. "Seroprevalence of Toxoplasma gondii IgG antibody in HIVinfected patients at the Lagos University Teaching Hospital". *HIV/AIDS –Research and Palliative Care* 3 (2011): 101-105.

9. Pawlowski J., *et al*. "Avaliação da memória de pacientes com lesão em núcleos da base e tálamo pós-AVC". *Psicologia em Pesquisa* 7.1 (2013): 79-88.

10. Weiss L M and Dubey J P. "Toxoplasmosis: A history of clinical observations". *International Journal for Parasitology* 39.8 (2009): 895-901.

11. Abedalthagafi M., *et al*. "Case Report Asymptomatic diffuse "encephalitic" cerebral toxoplasmosis in a patient with chronic lymphocytic leukemia: case report and review of the literature". *International Journal of Clinical and Experimental Pathology* 3.1 (2010): 106-109.

12. El Lakkis I., *et al*. "Association between latent toxoplasmosis and psychiatric disorders in HIV-infected subjects". *Journal of Acquired Immune Deficiency Syndromes* 68.1 (2015): e8-e9.

13. Chao C C., *et al*. "Effects of cytokines on multiplication of Toxoplasma gondii in microglial cells". *Journal of Immunology* 150 (1993): 3404-3410.

14. Creuzet, C., *et al*. "Neurons in primary culture are less efficiently infected by Toxoplasma gondii than glial cells". *Parasitology Research* 84.1 (1998): 25-30.

15. Melzer TC., *et al*. "Host cell preference of Toxoplasma gondii cysts in murine brain: a confocal study". *Journal of Neuroparasitology* 1 (2010): N100505.

16. Lyons R E., *et al*. "Toxoplasma gondii tachyzoite-bradyzoite interconversion". *Trends in Parasitology* 18.5 (2002): 198-201.

17. Berdoy M., *et al*. "The manipulation of rat behaviour by Toxoplasma gondii". *Mammalia* 59.4 (1995): 605-614.

18. Berdoy M., *et al*. "Fatal attraction in rats infected with Toxoplasma gondii". *Proceedings of the Royal Society of London B: Biological Sciences* 267.1452 (2000): 1591-1594.

19. Prandovszky E., *et al*. "The neurotropic parasite Toxoplasma gondii increases dopamine metabolism". *PLoS One* 6.9 (2011): e23866.

20. Money KM and Stanwood G D. "Developmental origins of brain disorders: roles for dopamine". *Frontiers in Cellular Neuroscience* 7 (2013): 260.

21. Denkers E Y., *et al*. "Manipulation of mitogenactivated protein kinase/nuclear factor-kappaB-signaling cascades during intracellular Toxoplasma gondii infection". *Immunological Reviews* 201 (2004): 191-205.

22. Vallochi A L., *et al*. "Molecular markers of susceptibility to ocular toxoplasmosis, host and guest behaving badly". *Clinical Ophthalmology* 2.4 (2008): 837-848.

23. Leng J., *et al*. "Toxoplasma gondii prevents chromatin remodeling initiated by Toll-like receptor-triggered macrophages activation". *Journal of Immunology* 182.1 (2009): 489-497.

24. Gazzinelli R T., *et al*. "Role of macrophage-derived cytokines in the induction and regulation of cell mediated immunity to Toxoplasma gondii". *Current Topics in Microbiology and Immunology* 219 (1996): 127-211.

25. Damsker JM., *et al*. "Th1 and Th17 cells: adversaries and collaborators". *Annals of the New York Academy of Sciences* 1183 (2010): 211-221.

26. Kebir H., *et al*. "Human T(H)-17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation". *Nature Medicine* 13.10 (2007): 1173-1175.

27. Prandota J. "Autism spectrum disorders may be due to cerebral toxoplasmosis associated with chronic neuroinflammation causing persistent hypercytokinemia that resulted in an increased lipid peroxidation, oxidative stress, and depressed metabolism of endogenous and exogenous substances". *Research in Autism Spectrum Disorders* 4.2 (2010): 119-155.

28. Prandota J. "Metabolic, immune, epigenetic, endocrine and phenotypic abnormalities found in individuals with autism spectrum disorders, Down syndrome and Alzheimer disease may be caused by congenital and/or acquired chronic cerebral toxoplasmosis". *Research in Autism Spectrum Disorders* 5.1 (2011): 14-59.

29. Parlog A., *et al*. "Toxoplasma gondii-induced neuronal alterations". *Parasite Immunology* 37.3 (2015): 159-170.

30. Stich O., *et al*. "An observational study of inflammation in the central nervous system in patients with bipolar disorder". *Bipolar Disorders* 17.3 (2014): 291–302.

31. Schroder N W and Schumann R R. "Single nucleotide polymorphisms of Toll-like receptors and susceptibility to infectious disease". *Lancet Infectious Diseases* 5.3 (2005): 156-164.

32. Al Nasr I., *et al*. "Toxoplasmosis and anti-Toxoplasma effects of medicinal plant extracts-A mini-review". *Asian Pacific Journal of Tropical Medicine* 9.8 (2016): 730-734.

33. Sonda S and Hehl A. "Lipid biology of Apicomplexa: Perspetives for new drug targets, particularly for Toxoplasma gondii". *Trends in Parasitology* 22.1 (2006): 41-47.

34. Oliveira CB., *et al*. "Pathogenicity and phenotypic sulfadiazine resistance of Toxoplasma gondii isolates obtained from livestock in northeastern Brazil". *Memórias do Instituto Oswaldo Cruz* 111.6 (2016): 391-398.

35. Kaye A. "Toxoplasmosis: diagnosis, treatment, and prevention in congenitally exposed infants". *Journal of Pediatric Health Care* 25.6 (2011): 355-364.

36. Mendes NH., *et al*. "Epidemiological and serological profiles of ocular toxoplasmosis in the municipality of Natal, northeastern Brazil". *Transactions of the Royal Society of Tropical Medicine and Hygiene* 108.10 (2014): 656-661.

37. Aspinall TV., *et al*. "The molecular basis of sulfonamide resistance in Toxoplasma gondii and implications for the clinical management of toxoplasmosis". *Journal of Infectious Diseases* 185.11 (2002): 1637-1643.

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