MEDDOCS
Open Access Publisher

Journal of Community Medicine

Open Access | Research Article

Neurological manifestations due to congenital toxoplasmosis, verified through the literature integrative review

Sabrina Ramires Sakamoto[1]; Aline do Nascimento Benitez[2]; Joice Cristina dos Santos[2]; Tatiani Palhota Lozano[2]; Juliana Mendonça Ferreira[2]; Saulo Hudson Nery Loiola[2]; Italmar Teodorico Navarro[3]; Jancarlo Ferreira Gomes[4]; Katia Denise Saraiva Bresciani[2]*

[1]Department of Nursing, Educational Foundation of Penápolis, South America

[2]São Paulo State University (Unesp), School of Veterinary Medicine, Araçatuba

[3]Department of Preventive Veterinary Medicine, Londrina State University, South America

[4]Faculty of Medical Sciences, University of Campinas (UNICAMP), Campinas, São Paulo, Brazil and Laboratory of Image Data Science, Institute of Computing, South America

***Corresponding Author(s): Katia Denise Saraiva Bresciani**

São Paulo State University (Unesp), School of Veterinary Medicine, Araçatuba

Email: bresciani@fmva.unesp.br

Received: Aug 24, 2018

Accepted: Dec 28, 2018

Published Online: Dec 30, 2018

Journal: Journal of Community Medicine

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Abstract

Congenital toxoplasmosis is a protozootic disease with a worldwide distribution. The clinical manifestations can vary in severity and it affects several fetal tissues when the woman becomes infected during the gestational period. To identify the main neurological manifestations in congenital toxoplasmosis, an integrative review of the literature was carried out, consulting the Virtual Health Library, PubMed and Scientific Electronic Library Online (SciELO). Keywords selected for search of publications were: "(Toxoplasmosis) and (Toxoplasmosis) and (Neurologic Manifestations) and (Neurologic Manifestations)". The complete articles, with abstracts available and related to the research object, in Portuguese and English, from journals published in the last ten years were included in this study and those that were not available through the databases or in a review format were excluded. The search was performed on February 1ST, 2018, when five articles were selected, all indexed in PubMed. Through this review, the main manifestations associated with *T. gondii* infection were visual loss, hearing loss, convulsion and that one's related to Alzheimer's disease.

Keywords: Toxoplasma; Chorioretinitis; Zoonoses; Public Health

Cite this article: Sakamoto SR, Benitez AN, Santos JC, Lozano TP, Bresciani KDS, et al. Neurological manifestations due to congenital toxoplasmosis, verified through the literature integrative review. J Community Med. 2018; 2: 1010.

Introduction

Toxoplasmosis is a zoonosis in which evolutionary infectious forms of the protozoan *Toxoplasma gondii* can be transmitted by oral or congenital via. Most of cases, this infection is asymptomatic in humans, although, when acquired during pregnancy it can cause severe and irreversible damage to the foetus [1].

The infection at the second or third gestational trimester can result in the Sabin`s tetrad, with microcephaly, retinochoroiditis, cerebral calcifications and mental disorder and, the earlier contact with *T. gondii*, the fetal death is common [2].

Nowadays, the possibility of neurodevelopmental diseases and mental disorders associated to toxoplasmosis has been investigated, as reported in an investigation with 3440 participants, that toxoplasmosis increase in 4.86 fold the chances of patients develop autism. Other disorders with *T. gondii* infection correlation were schizophrenia (OR=3.34), attention deficit and hyperactivity (OR=3.02), Asperger syndrome (OR=2.49), antisocial personality (OR=1.81), obsessive compulsive (OR=1.69), and anxiety (OR=1.57) [3].

The burden of congenital and ocular toxoplasmosis are specially reported in Brazil, were the infection in humans and animals are widely prevalent and the severity of clinical presentations are higher than in other countries [4]. Accordingly, the lessons from brazilian research groups has provide data to understand the disease in the rest of the world [5].

The variety of direct and indirect burdens of *T. gondii* infection during pregnancy has motivated this study in order to compile the scientific literature on the major neurological manifestations in the people with congenital toxoplasmosis.

Methods

The scientific literature was integrative reviewed to report on a compiled structure the major neurological manifestations caused by congenital toxoplasmosis.

The present study was elaborated according to the sequential problem design pathways: establishment of the review theme as a question; sampling; definition of inclusion and exclusion criteria; tabulation of the studies (identification of information's to be collected from studies using defined criteria and guided by instrument); analysis of the results, with identification and interpretation of conflicts and similarities and finally discussion of results and conclusion [6].

The review theme was elaborate on the question: "What are the major neurological effects caused by toxoplasmosis reported in the literature?" according the Population, Intervention, Comparison and Outcomes (PICO) strategy [7].

Sampling used the Health Virtual Library (Biblioteca Virtual de Saúde- BVS), PubMed and Scientific Electronic Library Online (Scielo) databases, on February 1st, 2018.The Key terms-(Toxoplasmose) and (Toxoplasmosis) and (Manifestações neurológicas) AND (Neurologic Manifestations) were determine by (Descritores de Ciências da Saúde -DeCS), available at [decs.bvs.br].

Inclusion and exclusion criteria included original research, entirely on line free available, in Portuguese or English languages, from journal indexed at least in one of the BVS, PubMed and Scielo databases, published from 2007 to 2017. Reviews and duplicates were excluded (Figure 1).

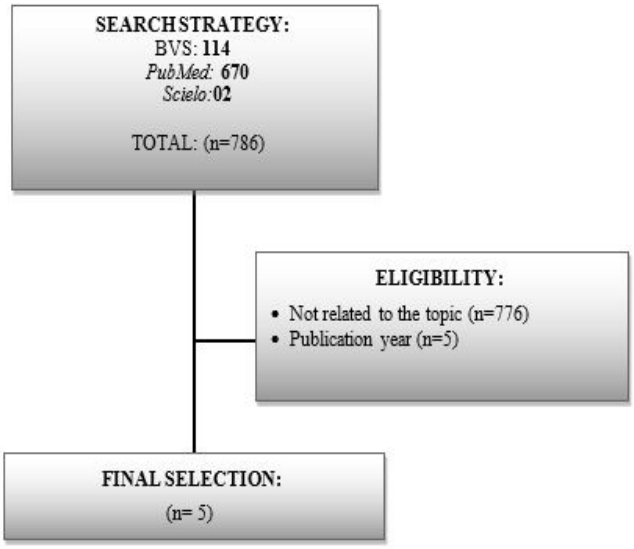

Figure 1: Flow diagram of the study design process of an integrative literature review on neurological manifestations associated to congenital toxoplasmosis, 2018.

Results

This integrative review selected five published articles, all extracted from PubMed database, homogenous temporal distributed in 2010, 2012, 2013 and 2017.

To organize the information during the data extraction, a table was created with the publication year, first author, title, aim, study design and major results of each article (Table 1).

The association of congenital toxoplasmosis with visual and hearing impairment was reported by two and one publishes studies, respectively. The influence of *T. gondii* metabolic products at central nervous system as causative of seizures and Alzheimer's disease protector were demonstrated through experimental researches with murine models, by other two publications.

Discussion

The integrative literature review allows searching, criticizing and synthesising knowledge in order to expand it, directed by evidence-based knowledge. Through that methodology, it is possible to gather the considerations reported by multiple studies on a specific topic (Mendes; Silveira; Galvão, 2008). In this research it was related five studies, all of them published in different years. It has shown that the approach of neurological manifestations of congenital toxoplamosis during these years had no particular preferences on some specific path of viewing (Table 1). In the first article, published in 2010, it was reported the ocular manifestations evidenced between the years 2000 to 2004, the first ophthalmological examination performed in 44 children up to 12 months with congenital toxoplasmosis, living in different regions of the state of Rio Grande do Sul [8].

In the second report on ocular manifestations due to congenital toxoplasmosis, which has published in 2017, the occurrence of toxoplasmosis associated with visual impairment was reported in eight patients, attended between 2012 and 2013, for the first ophthalmic evaluation at a hospital in Turkey [9].

The studies diverged on the mean age of the patients with congenital toxoplasmosis to the first medical ophthalmologic evaluation, which in Brazil occurred with 4.2 months, while in Turkey, it was 25 years. It also demonstrated low variability be-

tween the frequencies of Brazilian (70.4%) and Turkish (75.0%) patients; however, the occurrence of retinocoroiditis was 5.9 times higher in children than in adults. In addition, in 22/44 (50.0%) of the children other alterations such as cataract, microphthalmia, nystagmus and strabismus were found.

The differences reported between the articles may be associated to *T. gondii* predominant genotype in animals and humans in Brazil that presents higher virulence compared to the genotypes in other countries. The Brazilian genotype was incriminated as responsible for neurological issues such as hydrocephalus, microcephaly, and mental retardation in 35% of children who acquired congenital toxoplasmosis, and also for ocular and hearing impairment in 80% and 40% of them, respectively.

Through the interpretation of the results pioneer reported by Brazilian researches, it was possible to elucidate the association of the severity and development of the disease with de parasite's genotype, as well as ocular manifestations in postnatal infections, the influence of the immune responses on the pathogenesis, the development of lesions in the retina before the retinochoroiditis and adoption of medicamental prophylaxis in recurrent lesions. Despite the difference in the presentation of ocular toxoplasmosis in Brazil, there are no reasons to differentiate the bases of the disease among the countries [5].

Hearing impairment was the aim of the third article selected through this integrative literature review. Clinical and histopathological findings were observed in temporal bones of 3/9 (37.5%) newborns that came to death for congenital toxoplasmosis in Costa Rica with *T. gondii* cysts in brain tissue. The cystic form of the parasite does not develop typical formation of necrotic tissue, was located in the temporal bone of two individuals and, in the internal auditory canal, the tachyzoite was associated with inflammatory cells [10].

From these data, the hearing impairment associated to congenital toxoplasmosis was suggested as a product of postnatal tissue inflammation. It was confirmed in a study which hearing impaired were reported in 28% of children who were not treated or who received limited treatment. However, the number of deaf children was reduce to zero when antiparasitic therapy was introduce before 2.5 months of age and maintained for 12 months, which demonstrates the importance of early therapeutic strategies to promote the earlier clinical resolution of the deafness in the postnatal infections [11].

Other relevant aspects are neurological manifestations in chronic toxoplasmosis, which involves neurodevelopmental diseases such as autism, in response to persistent neuro inflammation, Down syndrome and Alzheimer's disease in response to neurodegeneration [1]. Neuropathy cases were covered by this integrative literature review in two articles in which were discussed the experimental inoculation of *T. gondii* in murine model, the first article focus on Alzheimer's Disease (AD) [12] and the second related to seizures associated to toxoplasma infection [13].

The deposition of β-amyloid plaques in the cortex and hippocampus of mice reduced markedly in those with AD and infected with *T. gondii* when compared to the control ones. Mice inoculated with *T. gondii*, developed higher anti-inflammatory cytokine levels when compared to negative control, even when inflammatory mediators remain unchanged and between de tests it was possible to detect delayed cognitive abilities in uninfected rats compared to infected mice, demonstrating the pathogenesis of immunosuppression induced by *T. gondii* infection as a protective factor for AD [12].

The correlation between the occurrence of *T. gondii* infection and the progression of AD was also reported as neglected in a case-control serological study with 75 patients and 75 healthy volunteers [14]. However, through the experimental inoculation of *T. gondii* in wild mice, it was verified that the disease can induce advanced AD signs such as olfactory reduction, anxiety, spatial memory loss, and lack of social recognition, and that could lead to AD in some individuals with underlying health problems [15].

Thus, there is strong evidence that *T. gondii* infection is associated with AD, however, the divergence between the results reported in the literature, requires further studies to conclude how this association is established.

Convulsive episodes in toxoplasmosis are reported in immunocompromised adults [16], immunocompetent teens [17], and newborns [18], showing that the disease is common to several types of individuals.

When the available reports with this variable were analyzed, it was estimated that risk of developing epilepsy was 2.25 times higher in patients with toxoplasmosis and a lack of research on convulsions in individuals infected by *T. gondii* [19] was demonstrated. Thus, the second article describing an experimental study with a neurological approach on toxoplasmosis contributes to the establishment of new knowledge about pathogenic mechanisms of this infection.

The article reported differences obtained by a study with the distribution of excitatory glutamatergic presynaptic proteins in healthy and *T. gondii* infected mice and indicated the loss of synaptic terminals in infected mice with seizures. The response to drug-induced convulsions against different strains of *T. gondii* was detected [13].

Through this integrative literature review, despite the limitations of articles selected by this methodology, it was possible to corroborate that ocular, hearing and neurodevelopmental impairment are the major health problems associated to congenital toxoplasmosis, and to demonstrate the recent reports associated with these disease.

Tables

Table 1: Characteristics of the included studies in the integrated literature review on neurological manifestations associated to congenital toxoplasmosis, according to the year of publication, first author, article's title, aim and major results, 2018.

Year	Author	Title	Aim	Major results
2010	J Melamed et al.	Ocular manifestations of congenital toxoplasmosis	To evaluate the ocular manifestations of congenital toxoplasmosis at the first ophthalmological examination of children up to the age of 12 months.	The ocular involvement was presented 31/44 (70.4%) children evaluated and 29/31 (65.9%) had retinochoroiditis lesions. These lesions were bilateral in22/29 (75.8%) patients and unilateral in 7/29 (24.2%), and most of than were concentrated in the papillomacular area. The retinochoroiditis lesions were active in 8(15.7%) eyes and had healed in 43 (84.3%). Other associated ocular alterations were present in 22/44 (50,0%) children, the most prevalent being 12/22 (54,54%) strabismus, 7/22 (31,82%) nistagmo, 6/22 (27,27%) cataract and 5/22 (22,73%) microphthalmia.
2012	Bong-Kwang Jung et al.	Toxoplasma gondii Infection in the Brain Inhibits Neuronal Degeneration and Learning and Memory Impairments in a Murine Model of Alzheimer's Disease	To determine the effect of the immunosuppression induced by T. gondii infection on the pathogenesis and progression of Alzheimer's Disease (AD) in Tg2576 AD mice.	Whereas the level of IFN-c was unchanged, the levels of anti-inflammatory cytokines were significantly higher in T. gondii-infected mice than in uninfected mice. Nitrite production from primary cultured brain microglial cells was reduced by the addition of *T. gondii*lysate antigen. The b-amyloid plaque deposition in the cortex and hippocampus of mouse brains was remarkably lower in *T. gondii*-infected AD mice than in uninfected controls. There are retarded cognitive capacities in uninfected mice as compared with infected mice.
2013	Mehti Salviz et al.	Otopathology in Congenital Toxoplasmosis	To describe the temporal bone histopathology in children with congenital toxoplasmosis.	Three of nine (33%) of the subjects presented parasites in the temporal bone. The organism was identified in the internal auditory canal, the spiral ligament, stria vascularis and saccular macula. The cystic form of the parasite was not associated with the inflammatory response seen in the active tachyzoite form. The hearing loss of toxoplasmosis is likely the result of a postnatal inflammatory response to the tachyzoite form of *T. gondii*.
2015	Justin M. Brooks et al.	Toxoplasma gondiil nfections Alter GABAergic Synapses and Signalingin the Central Nervous System	To show the excitatory glutamatergic presynaptic proteins in mouse infected with type II ME49 Toxoplasma tissue cysts.	While excitatory glutamatergic presynaptic proteins appeared normal, infection with type II ME49 Toxoplasma tissue cysts led to global changes in the distribution of Glutamic Acid Decarboxylase 67 (GAD67), a key enzyme that catalyzes GABA synthesis in the brain. *Toxoplasma*-infected mice develop spontaneous seizures and are more susceptible to drugs that induce seizures by antagonizing GABA receptors.
2017	Nedime Sahinoglu-Keşkek et al.	Causes of visual impairment in patients with ocular toxoplasmosis	To report the causes of visual impairment in patients with the classic clinical presentation of Ocular Toxoplasmosis (OT).	The mean age of the five (62.5%) women and three (37.5%) men was 25.7±7.6 years. In this study, visual impairment in majority of the patients was found to be related to vitreous cells and flare. Dense vitritis on macula scans and visual impairment were seen in the patients who had an active lesion closer to the fovea. SOCT may provide objective data of the cellular load of the eyes with posterior segment inflammation.

References

1. Bresciani KDS, Galvão ALB, Vasconcellos AL, Soares JA, Matos LVS, et al. Relevant aspects of human toxoplasmosis. Res J of Infec Dis. 2013; 7.
2. Mitsuka-Breganó R, Lopes-Mori FMR, Navarro IT. Toxoplasmose adquirida na gestação e congênita: vigilância em saúde, diagnóstico, tratamento e condutas [online]. Londrina: EDUEL. SciELO Books. 2010; 62.
3. Flegr J, Horáček J. Toxoplasmosis, but not borreliosis, is associated with psychiatric disorders and symptoms. Schizophr Res. 2018; 17: 30057-30064.
4. Dubey JP, Iago EG, Gennari SM, SU C, Jones JL. Toxoplasmosis in humans and animals in Brazil: high prevalence, high burden of disease, and epidemiology. Parasitol. 2012; 139: 13751424.
5. Grigg ME, Dubey JP, Nussenblatt RB. Ocular Toxoplasmosis: Lessons from Brazil. Am J Ophthalmol. 2015; 159: 999-1001.
6. Whittemore R, KnaflK. The integrative review: updated methodology. J Adv Nurs. 2005; 52: 546-553.
7. Santos CMC, et al. A estratégia pico para a construção da pergunta de pesquisa e busca de evidências. São Paulo: Rev Lat-Am Enf. 2007; 15: 508-511.
8. Melamed J, Eckert GU, Spadoni VS, et al. Ocular manifestations of congenital toxoplasmosis. Eye. 2010; 24: 528-534.
9. Sahinoglu-Keşkek N, et al. Causes of visual impairment in patients with ocular toxoplasmosis. J Infect Dev Ctries. 2017; 11: 192-195.
10. Salviz M, Montoya JG, Nadol JB, et al. Otopathology in Congenital Toxoplasmosis. Otol Neurotol Inc. 2013; 34: 1165-1169.
11. Brown ED, Chau JK, Atashband S, Westerberg BD, Kozak FK. A systematic review of neonatal toxoplasmosis exposure and sensorineural hearing loss. Int J of Ped Otorh. 2009; 73: 707-711.
12. Jung B-K, Pyo K-H, Shin KY, et al. Toxoplasma gondii Infection in the Brain Inhibits Neuronal Degeneration and Learning and Memory Impairments in a Murine Model of Alzheimer's Disease. PLoS ONE. 2012; 7: e33312.

13. Brooks JM, Carrillo GL, Su J, Lindsay DS, Fox MA, et al. Toxoplasma gondii Infections Alter GABAergic Synapses and Signaling in the Central Nervous System. M Bio. 2015; 6: e01428-e1515.

14. Mahami-Oskouei M, Hamidi F, Talebi M, Farhoudi M, Taheraghdam AA, et al. Toxoplasmosis and Alzheimer: can Toxoplasma gondii really be introduced as a risk factor in etiology of Alzheimer?. Parasitol Res. 2016; 115: 3169-3174.

15. Torres L, Robinson SA, Kim DG, Yan A, Cleland TA, et al. Toxoplasma gondii alters NMDAR signaling and induces signs of Alzheimer's disease in wild-type, C57BL/6 mice. J Neuroinflam. 2018; 15: 1-19.

16. Parekh P, Boggs JP, Silverberg M, Marik P. Seizure as an initial presentationn of human immunodeficiency virus: acute toxoplasmosis mimicking glioblastoma multiforme. Un Pres MC Dis. 2013; 14: 1-3.

17. Beltrame A, Venturini S, Crichiutti G, Meroni V, Buonfrate D, et al. Recurrent seizures during acute acquired toxoplasmosis in an immunocompetent traveller returning from Africa. Infection. 2016; 44: 259-262.

18. Yosr B, Karim A, Rania M, Olfa S, Aïda B, et al. Congenital Toxoplasmosis in Tunisia: Prenatal and Neonatal Diagnosis and Postnatal Follow-up of 35 Cases. The Am J Trop Med Hyg. 2018.

19. Ngoungou EB, Bhalla D, Nzoghe A, Dardé ML, Preux PM. Toxoplasmosis and Epilepsy-Systematic Review and Meta-Analysis. PLOS NTD. 2015; 19: 1-10.