RESEARCH ARTICLE

BEHAVIORAL CHANGES INDUCED BY TOXOPLASMOSIS IN ANIMALS AND HUMANS.

Murilo Abud Bichuette¹, Alvimar José da Costa¹, Ane Pamela Capucci Torres², Gláucio Luís Mata Mattos³, Guadalupe Sampaio Ferreira¹, Lucas Vinícius Costa Gomes³, William Marinho Dourado Coelho² and Katia Denise Saraiva Bresciani².

1. Centro de Pesquisas em Sanidade Animal, FCAV/UNESP, Jaboticabal, SP.
2. Departamento de Apoio, Produção e Saúde Animal, FMV/UNESP, Araçatuba, SP.
3. Empresa Brasileira de Pesquisa Agropecuária, EMBRAPA Suínos e Aves, Concórdia, SC.
4. Departamento de Clínica e Cirurgia Veterinária, FCAV/UNESP, Jaboticabal, SP.

Manuscript Info

Manuscript History

Received: 23 May 2017
Final Accepted: 25 June 2017
Published: July 2017

Key words:-
Toxoplasma gondii; behavior; disorders; rodents.

Abstract

In this literature review, we compiled information on the behavioral changes induced by toxoplasmosis in animals and humans. Pathologies due to toxoplasmic infection have been widely studied, but the chronic effects and modulation of the parasite-host interaction remain uncertain. In experimental infections of small rodents, behavioral changes have been investigated mainly through leakage parameters, assessment of motor sensory cognitive functions, as well as dopamine activity and release. Chimpanzees also showed behavioral changes, a phenomenon characterized, even, by specific aversion to their only predators. In adult humans, it has been proposed that tissue cysts exert behavioral changes in their hosts, either directly or through the release of metabolic products. Thus, chronic infection with Toxoplasma gondii has been associated with reduced motor reflex, increasing the risk of traffic accidents, as well as the inversion in personality, resulting in a lower score in the intelligence quotient (IQ), reduction in attainment Higher stages of schooling and, in the elderly, impairment of memory. Finally, it has been considered the hypothesis that dopamine may be involved in this process, since the psychomotor performance is lower in the infected individuals, still related chronic infection to Obsessive Compulsive Disorder, Parkinson's disease, suicide attempts, Autism, schizophrenia, Bipolar and Anxiety Disorders. Therefore, in this analysis, we demonstrate reports of scientific evidence of behavioral changes induced by both animal and human toxoplasmosis.

Copy Right, IJAR, 2017,. All rights reserved.

Introduction:-

Toxoplasma gondii, as intracellular protozoan, has felids as definitive hosts and among intermediate hosts, several warm-blooded animals (NICOLLE & MANCEAUX, 1909; FRENKEL & DUBEY, 1972). This parasite is located in the musculature and central nervous system, where it can cause behavioral changes (WITTING, 1979; YOLKEN et al., 2001; LAFFERTY, 2005) as a result of chronic infection (DENTILLO, 2013).
In humans the occurrence of the disease is high (ROBERT-GANGNEUX & DARDÉ, 2012), particularly in children (DUBEY et al., 2012), resulting in serious health consequences for their hosts (FLEGR, 2013). Studies have discussed host manipulation by the parasite and suggested that T. gondii infection may contribute to the onset of behavioral disorders in its intermediate hosts (SILVA & LANGONI, 2009; GATKOWSKA et al., 2013; GAKEWSKI et al., 2014). In this literature review, we compiled information on behavioral changes induced by toxoplasmosis in animals and humans.

**Behavioral Changes In Animals:**

- **Small rodents and chimpanzees:**

  Mice and rats, experimentally infected with T. gondii, presented lower learning and memory capacity in labyrinths, greater difficulty in accomplishing the stipulated routes and reduced activity on training days in relation to the control group (WITTING, 1979). This may be due to the direct physical effect of the cerebral cysts in the central nervous system, particularly in the limbic region, as well as the release of metabolites, leading to encephalitis (HOLLIMAN, 1997).

  Apathy has been observed simultaneously or coincidentally at the peak of pathological changes. In contrast, increased physical activity of rodents was verified precisely at the time of the chronicity of the disease, represented by the development of the brain cysts of T. gondii. Behavioral changes are only transient and disappear at approximately 12 weeks after inoculation of the parasite (HRDA et al., 2000).

  The hypothesis that Toxoplasma manipulates essential behaviors of its hosts to increase its own transmission has been well studied. The specific host-parasite interaction may alter the behavior of infected animals, increase the risk of predation and, consequently, the multiplication of the parasite through an increase in the number of transmission and life cycles (WEBSTER, 2001; LYTE, 2009).

  Rodents with toxoplasmosis demonstrate preference for cat and rabbit urines, in the circular arena (VYAS et al., 2007), with the confirmation of this hypothesis in the "Y" labirint (LAMBERTON et al., 2008). In a series of tests, mice chronically infected by avirulent type II (ME49) strain present motor and sensory deficits. In contrast, cognitive function, anxiety levels, social behavior, and motivation to explore new objects remain normal. The observed changes in behavior do not indicate severe brain damage and do not occur due to lesion in specific areas of the brain, which points out a subtle interaction of this parasite with its intermediate hosts and are suggestive of a greater predation due to this parasitic infection (GULINELLO et al., 2010).

  This parasitosis modifies neural activity in limbic brain areas necessary for innate defensive behavior in response to cat odor. In addition, this protozoan increases activity in limbic regions of sexual attraction when the rat is exposed to cat urine, a proof that this infection outweighs the innate fear response, causing it to develop a sexual attraction instead (HOUSE et al., 2011).

  Ratos infectados com Toxoplasma manifestam sintomas similares à esquizofrenia, apresentam redução na aprendizagem e na capacidade de memória, além de depressão (WANG et al., 2013).

  Mice have been used as a model to evaluate possible changes induced by T. gondii on the behavior of the host and to estimate its relation with the occurrence of psychiatric diseases in humans. In these animals, acute infection is accompanied by a decrease in noradrenergic system activity in females and a slight increase in some areas of males' brains. Infection induced elevation in serotonin and dopamine activity in acutely infected males (GATKOWSKA et al., 2013). Rats infected with Toxoplasma manifest symptoms similar to schizophrenia, present a reduction in learning and memory capacity, as well as depression (WANG et al., 2013).

  Chimpanzees infected with Toxoplasma gondii and kept in captivity in Gabon have shown a loss of innate aversion to the urine of leopards, their only natural predators. At the same time, they remained indifferent to the urine of humans, tigers and lions. The free parasite chimpanzees maintained their habitual behavior, that is, they showed repudiation of the urine of the leopards, but they normally approached the urine of the others. This result evidences not only a host-parasite modulation, but also indicates that this phenomenon occurs in a specific way, which increases the chance of prey encounter with its typical predator. The findings in these primates support the theory that the parasite also modulates the behavior of humans, especially when they are encased in the amygdala of the
limbic system, a region of the encephalon that is fundamental to self-preservation because it is the center of danger. (POIROTTE et al., 2016).

**Disorders In Humans:**

**Congenital infection:**
Pregnant women infected with T. gondii present temporary parasitemia, which may transmit the parasite to the fetus via the placental route and develop focal lesions in the placenta (DUNN, et al., 1999).

Early onset of autism symptoms in children correlates with the presence of rubella and toxoplasmosis during pregnancy (KOLVIN et al., 1971). Among the prenatal factors for the occurrence of West Syndrome (childhood epilepsy) is toxoplasmosis, which causes spasms, neuropsychic deterioration, and pathognomonic electroencephalogram with hypsarrhythmia (AGUIAR et al., 2003).

Depending on the gestational age at which the mother acquires the infection, there may be fetal death, hydrocephalus, intracranial calcification, chorioretinitis, auditory deficit and ocular lesions (DUNN, et al., 1999; ANDRADE, et al., 2008; PHAN, et al., 2008).

Social gestures and behaviors are learned through visual feedback (WRIGHT & SPIEGEL, 1999). Therefore, behavioral changes can be expected in children with visual problems resulting from transplacental transmission, who perform better in the social area and worse in the cognitive area (VITTA, 2001). In patients diagnosed with congenital toxoplasmosis and ocular lesions, concomitant neuroradiological changes should be suspected and investigated (MELAMED et al., 2001).

The toxoplasmic infection causes loss of vision in children, in the congenital form and if untreated in the first year of life, can promote the development of chorioretinal lesions even in adolescence. A good visual acuity is important in the normal physical and cognitive development of the human being (GRAZIANO, 2002).

Daughters of mothers with latent toxoplasmosis develop delayed ability to control head position, roll from supine position to prone position and crawl (KANKOVÁ et al., 2012).

**Behavior deviation caused by Toxoplasma in vehicle Drivers:**
The seropositive individual for T. gondii is more likely to be injured than non-infected ones, especially in cases of recent or protozoal infection (FLEGR et al., 2002). The production of dopamine is altered by the presence of cysts of this coccidia, and may be associated with brain tumor formation and personality disorder, resulting in decreased motor reflex and a greater propensity to become involved in traffic accidents (YERELI, 2006).

The action of parasite cysts seems to deteriorate drivers' reflexes, due to the alteration in neurotransmitter levels, with increased risk of accidents among individuals aged 31-44 years (KOCAZEYBEK et al., 2009), who have high titers of IgG against Toxoplasma (GALVÁN-ROMÁN et al., 2013).

**Personality disorders in men and women and learning Disorders:**
Based on the Cattell's Questionnaire, in the case of T.gondii infected individuals, men are more jealous, insecure, group dependent, and more confident, tolerant, and secure women (FLEGR et al., 1996) Mature and stable, with self-control, willpower and accuracy (FLEGR et al., 2000).

The change in the male psychological profile was also evaluated through the application of the Cloninger's Temperament and Character Inventory questionnaires and in the patients with latent infection by the parasite, there was a lower score in the novelty seeking and, moreover, it was verified that Are less likely to reach advanced stages of schooling (FLEGR et al., 2003).

In elderly individuals aged over 65 years, this coccidia was considered to be detrimental to memory and quality of life when evaluated through serology and specific questionnaires (GAKEWSKI et al., 2014).
Severe psychological changes in humans:-
Seropositive patients for T. gondii have lower psychomotor performance when compared to those free of infection. Although the mechanism is unknown, some authors assume that tissue cysts in the brain would be responsible for elevation in dopamine levels (HAVLÍČEK et al., 2001).

Studies suggest a correlation between the occurrence of chronic toxoplasmosis and obsessive-compulsive disorders (MIMAN et al., 2010a), Parkinson’s disease (MIMAN et al., 2010b), suicide attempts (YAGMUR et al., 2010), women in age groups more advanced ones corresponding to the postmenopausal years (LING et al., 2011), Schizophrenic patients (Baker et al., 2011) and bipolar disorder (HAMDANI et al., 2013) and anxiety (MARKOVITZ et al., 2014).

The development of Autism Spectrum Disorders (ASD) triggered by several factors associated with chronic neuroinflammation and metabolic alterations may be due to the chronic latent infection congenital or acquired by T. gondii (PRANDOTA, 2010). In addition, chronic latent infection by this parasite may reduce the sense of smell in patients with various neuropsychiatric and/or autoimmune diseases, and may contribute, at least in part, to the development of depression, often observed in these individuals (PRANDOTA, 2014).

Conclusion:-
In this review we present reports of scientific evidence of behavioral changes induced by toxoplasmosis in animals and humans. Although the effects of chronic infection are not fully understood, it is evident that dopamine is the main neurotransmitter involved in this phenomenon.

Referências:-
1. Aguiar, S.M.F.; Torres, C.P.; Borsatto, M.C. Síndrome de West. Jornal brasileiro de odontopediatria & odontologia do bebê. v.6, n.30, p.123-126, 2003.
2. Andrade, G. M. Q.; Resende, L. M.; Goulart, E. M. A.; Siqueira, A. L.; Vitor, R. W. A.; Januario, J. N. Deficiência auditiva na toxoplasmose congênita detectada pela triagem neonatal. Revista Brasileira de Otorrinolaringologia. v.74, n.1, p.21-8. 2008.
3. Dentillo, D. B. Toxoplasmose crônica pode manipular comportamento. Ciência e Cultura. v. 65, n.1, p.14-15, 2013.
4. Dubey J. P. History of the discovery of the life cycle of Toxoplasma gondii. International Journal for Parasitology. v.39, p.877-882, 2009.
5. Dubey, J.P.; Lago, E.G.; Gennari,S.M.; Su, C.; Jones, J.L. Toxoplasmosis in humans and animals: high prevalence high burden of disease, and epidemiology. Parasitology. v.139, 1375-1424, 2012.
6. Flegr, J.; Žítková, S.; Kodym, P.; Frynta, D. Induction of changes in human behavior by the parasitic protozoan Toxoplasma gondii. Parasitology. v.113, p.49-54, 1996.
7. Flegr, J.; Kodym, P.; Tolarová, V. Correlation of duration of latent Toxoplasma gondii infection with personality changes in woman. Biological Psychology. v.53, p.57-68, 2000.
8. Flegr, J.; Havlíček, J.; Kodym, P.; Malý, M.; Smahel, Z. Increased risk of traffic accidents in subjects with latent toxoplasmosis: a retrospective case-control study. Infectious diseases. v.2, n.11, p.1-6, 2002.
9. Flegr, J.; Preiss, M.; Klose, J.; Havlíček, J.; Vitáková, M.; Kodym, P. Decreased level of psychobiological factor novelty seeking and lower intelligence in men latently infected with the protozoan parasite Toxoplasma gondii dopamine, a missing link between schizophrenia and toxoplasmosis? Biological Psychology. v.63, p.253-268, 2003.
10. Flegr, J. Influence of latent Toxoplasma infection in human personality, physiology and morphology: pros and cons of the Toxoplasma-human model in studying the manipulation hypothesis. Journal of Experimental Biology. v.216, p.127-133, 2013.
11. Frenkel, J. K.; Dubey, J. P. Rodents as vectors for feline Coccidia, Isospora felis and Isospora rivolta. The Journal of Infectious Disease. v.125, n.1, p.69-72, 1972.
12. Galván-Ramírez,L.L.; Sánchez-Orozco, L.V.; Rodríguez, L.R.; Rodríguez, S.; Roig-Melo, E.; Sanromán, R.T.; Chiquete, E.; Armendáriz-Borunda, J. Seroepidemiology of Toxoplasma gondii infection in drivers involved in road traffic accidents in the metropolitan area of Guadalajara, Jalisco, Mexico. Parasites & Vectors. v.6, p.294, 2013.
13. Gatkowska J.; Wieczorek M.; Dziadek B.; Dzitko K.; Długonska H.: Sex-dependent neurotransmitter level changes in brains of Toxoplasma gondii infected mice. Experimental Parasitology. v.133, p.1-7, 2013.
14. Graziano, R.M. Exame oftalmológico do recém-nascido no berçário: uma rotina necessária. Jornal de Pediatria. v.78, n.3, p.187-188, 2002.

15. Gulinello, M.; Acquarone, M.; Kim, J. H.; Spray, D. C.; Barbosa, H. S.; Sellers, R.; Tanowitz, H. B.; Weiss, L. M. Acquired infection with Toxoplasma gondii in adult mice results in sensorimotor deficits but normal cognitive behavior despite widespread brain pathology. Microbes and Infection. v.12, p.528-537, 2010.

16. Hamdani, N.; Duban-Huard, C.; Lajnef, M.; Richard, J. R.; Delavest, M.; Godin, O.; Le Guen, E.; Vederine, F. E.; Lépine, J.P.; Jamain, S.; Houenou, J.; Le Corvoisier, P.; Aoki, M.; Moins-Teissier, H.; Charron, D.; Krishnamoorthy, R.; Yolken, R.; Dickerson, F.; Tamouza, R.; Leboyer, M. Relationship between Toxoplasma gondii infection and bipolar disorder in a French sample. Journal of Affective Disorders. v.148, p.444-448, 2013.

17. Havlíček, J.; Gasova, Z.; Smith, A. P.; Zvara, K.; Flegr, J. Decrease of psychomotor performance in subjects with latent ‘‘asymptomatic’’ toxoplasmosis. Parasitology. v.122, p.515-520, 2001.

18. Holliman, R. E. Toxoplasmosis, behavior and personality. Journal of Infection. v.35, p.105-110, 1997.

19. Holub, D.; Flegr, J.; Dragomirecka, E.; Rodriguez, M.; Preiss, M.; Nova K., T.; Čerma K., J.; Hora C’ek, J.; Kodym, P.; Libiger, J.; Ho’ Schl, C.; Motlova, L. B. Differences in onset of disease and severity of psychopathology between toxoplasmosis-related and toxoplasmosis-unrelated schizophrenia. Acta Psychiatrica Scandinavica. v.127, p.227–238, 2013.

20. House P. K.; Vyas, A.; Sapolsky, R. Predator Cat Odors Activate Sexual Arousal Pathways in Brains of Toxoplasma gondii Infected Rats. PLoS One. v.6, n.8, e.23277, 2011.

21. Hrda, S.; Votýpka, J.; Kodym, P.; Flegr, J. Transient nature of Toxoplasma gondii-induced behavioral changes in mice. Journal of Parasitology. v.86, n.4, p. 657-663, 2000.

22. Kanková, S.; Sulc, J.; Krivohlavá, R.; Kubena, A.; Flegr, J. Slower postnatal motor development in infants of mothers with latent toxoplasmosis during the first 18 months of life. Early Human Development. v. 88, p.879-884, 2012.

23. Kocazybek, B.; Oner, Y. A.; Turksoy, R.; Babur, C.; Cakan, H.; Sahip, N.; Unal, A.; Ozaslan, A.; Kilic, S.; Saribas, S.; Aslan, M.; Taylan, A.; Koc, S.; Dirican, A.; Uner, H. B.; Oz, V.; Ertekın, C.; Kucukbasmaci, O.; Torun, M. M. Higher prevalence of toxoplasmosis in victims of accidents suggest increased risk of traffic accident in Toxoplasma-infected inhabitants of Istanbul and its suburbs. Forensic Science International. v.187, p.103-108, 2009.

24. Kolvin, I.; Ounsted, C.; Humphrey, M.; Mcnay, A. The phenomenology of childhood psychoses. British Journal of Psychiatry. v.118, p.385-395, 1971.

25. Lafferty, K. D. Look what the cat dragged in: do parasites contribute to human cultural diversity?. Behavioural Processes. v.68, n.3, p.279-282, 2005.

26. Lamberton P. H. I.; Donnelly C. A.; Webster J. P. Specificity of the Toxoplasma gondii-altered behaviour to definitive versus non-definitive host predation risk. Parasitology. v.135, p.1143–1150, 2008.

27. Ling V. J.; Lester, D.; Mortensen, P. B.; Langenberg, P. W.; Postolache, T. T. Toxoplasma gondii seropositivity and suicide rates in women. Journal of Nervous and Mental Disease. v.199, n.7, p.440–444, 2011.

28. Lyte, M.; Gaykema, R. P. A.; Goehler, L. E.; Moselio, S. Behavior modification of host by microbes. Encyclopedia of Microbiology. p.121-127, 2009.

29. Markovitz, A. A.; Simanek A. M.; Yolken R. H.; Galea, S.; Koenen, C. K.; Chen, S.; Aiello, A. E. Toxoplasma gondii and anxiety disorders in a community-based sample. Brain, Behavior, and Immunity. in press. http://dx.doi.org/10.1016/j.bbi.2014.08.001. 2014.

30. Melamed, J.; Dornelles, F.; Eckert, G.U. Alterações tomográficas cerebrais em crianças com lesões oculares por toxoplasmose congênita. Jornal de Pediatria. v.77, n.6, p.475-480, 2001.

31. Miman, O.; Mutlu, E. A.; Ozcan, O.; Atambay, M.; Karlidak, R.; Unal, S. Is there any role of Toxoplasma gondii in the etiology of obsessive–compulsive disorder?. Psychiatry Research. v.177, 263–265, 2010a.

32. Miman, O.; Kusbeci, O.Y.; Aktepe, O.C.; Cetinkaya, Z. The probable relation between Toxoplasma gondii and Parkinson’s disease. Neurosciences Letters. v.475, p.129-131, 2010b.

33. Mosquera, C. F. F.; Teixeira, R. M. M. O diagnóstico do autismo e a construção da linguagem no ensino da arte inclusivo. Revista do Núcleo de Estudos e Pesquisas Interdisciplinares em Musicoterapia. v. 1, p. 1-141, 2010.

34. Nicolle, C.; Manceaux, L. Sur un protozoaire nouveau du gondi. Archives des Instituts Pasteur de Tunis. v. 54, n. 2, p. 216-218, 1909.

35. Okusaga, O.; Langenberg, P.; Sleemi, A.; Vaswani, D.; Giegling, I.; Hartmann, A. M.; Konte, B.; Friedl, M.; Groer, M. W. Yolken, R. H.; Rujescu, D. Postolache, T. T. Compared T. gondii plasma antibody titers and
seropositivity from two groups of patients with schizophrenia; one with and one without prior history of suicide attempt. Schizophrenia Research. v.133, p.150-155, 2011.

36. Patrick D. Gajewski, P. D.; Falkenstein, M.; Hengstler, J. G.; Golka, K. Toxoplasma gondii impairs memory in infected seniors. Brain, Behavior, and Immunity. v.36, 193-199, 2014.

37. Phan, L.; Kasza, K.; Jalbrzikowski, J.; Noble, A. G.; Latkany, P.; Kuo, A.; Mieler, W.; Meyers, S.; Rabiah, P.; Boyer, K.; Swisher, C.; Mets, M.; Roizen, N.; Cezar, S.; Remington, J.; Meier, P.; Mcleod, R. Longitudinal study of new eye lesions in children with toxoplasmosis who were not treated during the first year of life. American Journal of Ophthalmology. v.146, n.3, p.375-384, 2008.

38. Phan, L.; Kasza, K.; Jalbrzikowski, J.; Noble, A. G.; Latkany, P.; Kuo, A.; Mieler, W.; Meyers, S.; Rabiah, P.; Boyer, K.; Swisher, C.; Mets, M.; Roizen, N.; Cezar, S.; Remington, J.; Meier, P.; Mcleod, R. Longitudinal study of new eye lesions in children with toxoplasmosis who were not treated during the first year of life. American Journal of Ophthalmology. v.146, n.3, p.375-384, 2008.

39. Prandota, J. Possible link between Toxoplasma gondii and the anosmia associated with neurodegenerative diseases. American Journal of Alzheimer's Disease and Other Dementias. v.29, n.3, p.205-14, 2014.

40. Robert-Gangneux, F.; Dardé, M.L. Epidemiology and diagnostic strategies for toxoplasmosis. Clinical Microbiology Reviews. v.25, n.2, p.264-296, 2012.

41. Silva, R. C.; Langoni, H. Toxoplasma gondii: host–parasite interaction and behavior manipulation. Parasitology Research. v.105, p.893–898, 2009.

42. Vitta, F.C.F. Avaliação terapêutica ocupacional de crianças com encefalopatias crônicas infantis não progressivas (ECInP). Caderno de Terapia Ocupacional UFSCar. v. 9, n. 2, p. 106-112, 2001.

43. Yagmur, Fatih.; Yazar, S.; Temel, H.O.; Cavusoglu, M. May Toxoplasma gondii increase suicide attempt-preliminary results in Turkish subjects?. Forensic Science International. v.199, p.15-17, 2010.

44. Yereli, K.; Cuneyt Balcioglu, I.; Ozbilgin, A. Is toxoplasma gondii a potential risk traffic accidents in Turkey? Forensic Science International. v.163, p.34-37, 2006.