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RESEARCH ARTICLE

BEHAVIORAL CHANGES INDUCED BY TOXOPLASMOSIS IN ANIMALS AND HUMANS.

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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.

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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).

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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 a the "Y" labirint (LAMBERTON et al., 2008). In a serie 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 (KOCZEYBEK *et al.*, 2009), who have high titers of IgG against *Toxoplasma* (GALVÁN-RAMÍREZ *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 (GAKIEWSKI *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.

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