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Reactivation of Latent Toxoplasmosis Leading to Behavioral Changes

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Abstract

It is well-known that the number of people owning cats in their houses and feeding them on the streets is high. The high number of cats owned by households in Turkey in 2019 was estimated to be 3.8 million. A great number of stray cats are fed and taken care of by the neighborhood residents in all the regions of Turkey and it is almost impossible to offer an estimation about the exact number of these animals, but it is fair to say that the cumulative number is very large.

The cats and the other felids are the only known definitive host of this protozoan parasite that infects most species of warm-blooded animals, including humans.

In humans, acute infections with Toxoplasma gondii during pregnancy and its potentially deleterious effect on the fetus and the newborn are well known and properly considered by the obstetricians.

Despite occasionally observed neurological changes, T. gondii chronic infections were usually considered largely innocuous in the otherwise healthy non pregnant patients.

However, more recent studies on felids have suggested that behavioral changes are sometimes manifests during the latent infections with this parasite. Similar changes have also been reported in human beings.

Hence, we reviewed reports about the central nervous system involvement in animals and human beings and suggested that it will be appropriate to consider "toxoplasmosis" in differential diagnosis while dealing with medical problems associated with behavioral changes of members of the human population in Turkey. We have; therefore, enumerated the conditions that fall into this category.

Keywords: Toxoplasmosis, infection, cat, diagnosis, reactivation, parasite, disease

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Background

T. gondii has an indirect life chain. The cat is the only definitive host that can disperse the eggs of this parasite in feces. In soil contaminated with cat feces, oocysts can survive for one year. If these oocysts are eaten by another cat, living organisms emerging from the oocysts in that cat's intestine invade the intestinal wall epithelium and both sexual and asexual cycles take place. On the other hand, if these oocysts are eaten by a creature other than the cat, an extra-intestinal cycle takes place and asexual reproduction occurs in this cycle. In this way, small and thin-walled cysts are formed in the nucleated cells of the host. This event takes place especially in brain cells. If a cat infected with toxoplasma, eats the intermediate host that has eaten an object, such as a mouse, the life chain of T.gondii is complete.

There are four types of diseases associated with Toxoplasma:

1. Congenital Toxoplasmosis: This is passed from the infected mother to the developing baby in the womb. Serious malformations including microcephaly, intracerebral calcification, and miscarriage may occur.
2. Acute postnatal Toxoplasmosis: Tachyzoites (rapid dividing parasite cells) are seen in blood and tissues. Symptoms such as enlarged lymph nodes, fever and headache usually suggest a mild viral infection. Serious neurological complications that rarely result in death can also be seen in this type of infection.

3. Chronic Toxoplasmosis: People become infected if they eat meat that is undercooked and these meats have thin-walled oocysts of Toxoplasma. In this case, acute Toxoplasmosis symptoms are seen for a long time.

4. Latent Toxoplasmosis: When the parasite is acquired in any way, it continues to exist as dormant but alive bradyzoites in the cysts it forms in the tissues throughout the life of the host. Bradyzoids may activate and cause serious neurological damage in diseases where the host is immunosuppressed as a result of a disease such as AIDS, or when chemotherapy is used. (2)

Reactivation and Primary Infection

When toxoplasmosis occurs for the first time in AIDS patients, a systemic toxoplasma infection is seen, including the lung, liver, bone marrow, heart, stomach, and brain. (3) On the other hand, if there is a reactivation of toxoplasmosis, the lesions are located in the brain.

A similar distribution is also seen in animal models. (4) Patients showing serological features of latent toxoplasma (IgG positive, IgM negative) may have body-dispersed toxoplasmosis (5). Chorioretinitis seen in congenital toxoplasmosis is also rarely seen in immunosuppressed patients (6).

Toxoplasma cysts located in the tissues continue their existence in the brain and muscles in the chronic phase and lead to the development of a life-long protective immunity against infections that may occur after that. (7)

Mollaret meningitis, especially seen in women, is characterized by recurrent episodes of headache, transient neurological anomalies, and the presence of mononuclear cells in the cerebrospinal fluid. This condition is usually encountered in the presence of HSV-2. J. Prandota stated that recurrent headaches, which are also seen in

HIV-uninfected patients, may be the result of acquired cerebral toxoplasmosis. (8)

Behavioral Changes Caused by Toxoplasmosis Infections in Rodents

It is known that Toxoplasma gondii infections cause some effects on the brain of rodents, preventing these animals from being afraid of cats, thus leading to the possibility of the parasite being eaten by the cat.

Observations made in nature and in the laboratory are important for reflecting the wild rats being the permanent intermediate host.

Although rats have impulses that cause them to escape from areas with symptoms reflecting the presence of cats, we see that this has changed as a result of the effect of T. gondii, and even this innate escape response turns into an attraction.

It has been determined that the change caused by T. gondii infection was limited to the cat's odor.
Toxoplasma-infected rats behaved differently in areas contaminated with their own odor, in areas with neutral odors, and in areas with rabbit odour. This shows that the change in rats infected by T. gondii is not a result of a deterioration in the olfactory abilities of these animals, but consists of a cognitive change that occurs against the animal that poses a risk due to the effect of T. gondii. (9)

According to the Manipulation Hypothesis, a parasite can change the behavior of its host in a way that suits its interests. According to the proponents of this thesis, this behavioral change in the host is not an accidental side effect of infection, but a result of the evolution of the parasite. (9)

There are other parasites that cause changes in their hosts according to their purposes: For example, Ophiocordiceps unilateralis, known as the "Zombie Ant fungus", invaded the brains and muscles of some ants in the forests of Brazil, leading them to leave their nests and to cling on one of the leaves of a plant at a height of 25 cm from the ground. This height is the optimal temperature and humidity level for the growth of the fungus. Under this ideal condition, the fungus multiplies inside the ant and feeds on what the host eats. (10)

It has been observed that rats approach cats without fear when the normally anxiogenic (anxious) NMDA receptors in the amygdala in the brain are blocked.(11)

The fact that the amygdala plays a role in the development of memory and emotional reactions such as fear may be why mice infected with these regions may exhibit an avoidance or modified fear or even sexual arousal response to cat odor. According to the Manipulation Hypothesis, in this context, the parasite creates a desire to turn to the cat instead of the innate fear of cats in the mouse, but does not change the other characteristics of the mouse.

A study linking all areas of the brain that are infected with changes in behavior have not been done yet.

Piekarski and Witting observed a decrease in memory and learning capacity in mice injected with T. gondii compared to uninfected mice. (12)

Hay and Hutchinson et al. examined the effects of postnatal and congenital toxoplasmosis on the activities and foraging behaviors of laboratory mice and found that the infected ones were more active. A greater tendency not to hide was also observed in infected mice. (13)

These researchers repeated their experiments using laboratory rats and observed that although some rats had reduced

learning ability, it was less than that seen in laboratory rats.

As Joanne P. Webster et al. explained these differences in latent toxoplasmosis, the brain of mice is more extensively infected than that of rats and in the acute phase, infection in mice has a greater potential to cause morbidity. (14)

According to this source, Toxoplasma gondii increases the amount of dopamine in rodents. This proliferation may occur as a result of the secretion of inflammatory substances by increasing the levels of cytokines such as dopamine such as interleukin-2 or directly produced by the parasite. Many of the neurobehavioral symptoms described by toxoplasmosis may also be linked to the overall function of dopamine in the brain.

In addition to studies reflecting the effect of Toxoplasma infection on behavior, there are also studies that do not confirm these findings. Among these, there are also researchers who claim that it does not affect memory (15), does not affect The differences in the methods of infection (intraperitoneal syringe, congenital or oral) of the rodents used in the experiments are also striking. It has been suggested that this may affect the host's immune response and, in this way, the consequences of infection. (18)

Decreased Immunity in Elderly and Toxoplasmosis

Aging leads to a decline in immune systems. This is associated with disruption of T cells and the antigen repertoire in both humoral and cell-mediated immune responses. (19)

Elderly persons are likely to exhibit clinical manifestations due to reactivation of T. gondii infection. Relapse of congenitally acquired T. gondii retinochoroiditis is more likely in people older than 40 years of age.

The probability of infection increases in relatively hot and humid climates and with advancing age. (20)

Humans can be more easily infected by T. gondii as a result of decreased immunity with age. Significant changes occur in the cellular immune component in old age: There is a decrease in the THI subgroup, which plays an important role in resistance against intracellular parasites. Older mice are less resistant to T. gondii infections and die from these infections more often than younger mice. Looking at these findings, it can be thought that the same thing may apply to older people. Toxoplasma seropositivity increases in elderly people.(21)

Clinically significant reactivations of T. gondii infections are more likely to occur in the elderly.

The Role of Toxoplasma Reactivation in Differential Diagnosis:

Changes in Behavior and Personality

People infected with Toxoplasma showed different personality profiles from those who were not infected when examined with two versions of Cattel's 16PF, Cloninger's TCI and Big Five questionnaires.

According to the researchers, the difference between the two groups increased over time after infection. It has been argued that what is at issue here is not that human personality increases the probability of infection, but that toxoplasma infection affects one's personality.

A prospective review involving three retrospective and multiple case and control groups, reflected that infection

with toxoplasmosis prolongs the human reaction time. It has been suggested that these findings may explain the increased probability of infected persons to have traffic accidents.

There are many studies reflecting the increased incidence of toxoplasma in schizophrenic patients: Toxoplasma-infected schizophrenic patients differ from schizophrenic patients uninfected with toxoplasma by brain anatomy findings and more pronounced symptoms of the disease. (22)

In humans, no causal link between toxoplasma infection and car accidents has been identified to date, but correlative data are plentiful. For example, 33% of 185 car drivers who were not intoxicated and had a car accident who were evaluated in a 6-month period in Turkey were found to have had a toxoplasma infection. (23)

We see that latent T. gondii infections rarely coexist with acute pathology, but such infections are increasingly found in automobile accidents, neuroticism and suicide cases, and this relationship is explained by personality changes that result in risk taking. (24)

In some studies, seropositivity was found for toxoplasma in schizophrenia and other severe psychiatric diseases, but consistent results could not be obtained regarding correlation. Toxoplasma gondii may present with symptoms specific to schizophrenia with encephalitis and other psychiatric diseases. Dreaming, thinking disorder, and auditory hallucinations have been observed in patients with AIDS and Toxoplasma encephalitis. (25)

Conclusion

There are studies reflecting that reactivation of latent toxoplasmosis can lead to behavioral and personality changes in humans as well as in many rodents. In this case, it is clear that the possibility of toxoplasmosis in certain diseases should be considered in the differential diagnosis. Studies that reinforce the idea that this fact should be taken into account, especially in our country where cats are widely fed, have been reviewed.

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