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THE EFFECTS OF TOXOPLASMA GONDII INFECTIONS ON ANXIETY, DEPRESSION AND LEARNING IN OFFSPRINGS OF INFECTED PARENTS

ABSTRACT

Toxoplasma Gondii is a zoonotic parasite showing intracellular localization. Although it doesn't select a specific region in the brain tissue, the cyst forms occurring in the chronic phase may cause behavioral changes when it is located in the brain regions related to behavior. The aim of this study is to investigate whether there is a relationship between neurodegenerative and neuropsychiatric diseases caused by antibodies transmitted to the first generation of T.Gondii infection by behavioral tests. In this study, using a total of 24 female and 6 male rats. Behavioral tests have been applied to F1 generation groups female and male. In this study, female rats with chronic T.Gondii infection have been found to have increased anxiety in open field in the first generation male offsprings and decreased locomotor activity. Increased mobility in male offsprings has been observed in the elevated plus maze test. In female offspring, it has reduced anxiety and depression.

Keywords: Toxoplasma Gondii, Behavior, Anxiety, Memory, Learning

1. INTRODUCTION

Toxoplasma Gondii is a zoonotic parasite showing intracellular localization. Approximately one-third of the world's population is reported to be infected with T.Gondii (Dubey and Jones, 2008). Depending on the eating habits of societies, the incidence of this parasite varies (Montoya and Liesenfeld, 2004). This parasite which cats are the last host, is transmitted by the oocysts excreted by the feces of the cats and taken by humans and other mammals by water and food incidentally and infection is formed. In the biology of the parasite there are three infective phases known as tachyzoites, bradyzoites (in tissue cyst) and sporozoites (in oocyst) (Khan, Dubey et al. 2011). Tachyzoites are placed in every cell of the body especially in organs such as brain, eye, muscle, liver by the way of placenta and the acute phase toxoplasmosis is formed. The forms that pass into bradyzoites phase by settle in the organs and, form a cyst after a period of 2-3 days and pass into the latent period. It can be carried in the body for a long time without any symptoms. During the latent period, it remains in this form for many years. There are only symptoms at the molecular level during this period. However, in cases

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such as AIDS, immunosuppressive treatment, stress, which causes the immune system suppression, these cysts become activated and leave the bradyzoites in the environment and re-forms the tachyzoites. In the cells of the intermediate hosts, the tachyzoite (Rorman, Zamir et al. 2006), which has the ability to rapidly proliferate, proliferates asexually with the endodyogeny repeating every 5-9 hours in the host cell. When the immune system is formed against parasite, tissue cysts are formed in various tissues. Some placental proteins expressed differently in the placenta of infected mice have been found and these proteins have been associated with different biological processes during pregnancy, especially during the trophoblast invasion. The findings have provided explaination for the molecular mechanisms of abnormal pregnancy outcomes caused by T.Gondii infection(Jiao, Zhang, et al., 2017).Different studies have found that several immune cells and molecules participate in abnormal pregnancy outcomes caused by T.Gondii infection (Harker, Ueno et, al., 2015). Different studies have found that several immune cells and molecules participate in abnormal pregnancy outcomes caused by T.Gondii infection (Xu, Zhao, et al., 2013; Liu, Zhao, et al., 2014; Liu, Zhao, et al., 2014).

It has been reported that congenital toxoplasmosis affects mental functions in humans; causes hydrocephalus and intracranial calcification (Caiaffa, Chiari, et al., 1993; Flegr, 2013)decreasing telectual function, and observing mental retardation in 9% of them (Caiaffa, Chiari, et al., 1993). Latent toxoplasmosis shows different immunmodulator effects in men and women (Flegr, Lenochová, et al., 2011). It has been shown that people who have the blood group Rh positive have a protective effect against latent toxoplasma infection and makes ineffective the infection reaction time (Novotná, Havlíček, et al., 2008)and personal change (Flegr, Lenochová, et al., 2011). The rate of causing schizophrenia in women is higher than in men (Yolken, Dickerson, et al., 2009; Wang, Xiang, et al., 2014). Latent toxoplasmosis causes neurological diseases such as obsessive-compulsive disorder (OCD), Parkinson's disease (Miman, Kusbeci, et al., 2010), Alzheimer's disease (Kusbeci, Miman, et al., 2011), autism(Prandota, 2011)and suicide attempts (Arling, Yolken, et al., 2009, Wang, Li, et al., 2013)in addition, drugs used in patients with bipolar disorder are thought to reduce the growth of T.Gondii in vitro (Xiao, Kannan, et al., 2012).

2. RESEARCH SIGNIFICANCE

The effects of acute T.Gondii infection have been investigated, it has been reported the effects especially on the fetus and newborn during pregnancy. Despite the investigation of the effects of chronic T.Gondii infection, it is not yet clear. Studies have shown that it can affect many biological processes caused by changes in proteins in the acute period. These processes can cause different processes until the chronic period. It is very important to investigate the genetic and epigenetic causes of hormonal, immunological changes caused by infection in host cells of future generations. In this study, it was aimed to show that chronic infection may be effective on some cellular mechanisms on the offspring and to raise awareness about this disease.

3. MATERIALS AND METHOD

3.1. Animals

The experimental animals used in the study were obtained from the Experimental Animal Research Center of BAIBU. The animals were kept in an Experimental Animal Application Research Center for 12

hours of light/dark, relative humidity of 60-70% and fed ad libitum during the study.

3.2. Experimental Groups

In this study, 2-4 months old Wistar Albino Rats, 32 female and 8 male rats were used as parents. Each male and half of the female rats was injected intraperitoneally with $1x10^4$ tachyzoites in per millilitre to create T.Gondii infection (Ribeiro, Pereira, et al., 2004). Three months after, all parent rats were divided into four different groups for mating. The first parental group (G1) consists of 8 infected females and 2 non-infected male rats. The second parental group (G2) consists of 8 non-infected female and 2 infected male rats. The third parental group (G3) consists of 8 infected females and 2 infected male rats. The fourth parental group (G4) is the control group and consists of 8 non-infected female rats and 2 non-infected male rats. The offspring obtained from all parental groups were considered to be the first generation (F1) offspring. Offsprings obtained from the first group (G1-F1) were divided into two groups as 8 male and 8 female. The offsprings obtained from other groups were named G2-F1, G3-F1 and G4-F1 respectively. After two months of age, the offsprings were tested for behavioral tests for measuring learning-memory, anxiety and depression level. Because the number of offspring obtained from the third group could not be obtained sufficiently, it could not be included in behavioral tests.

3.3. Experimental T.Gondii Infection

T.Gondii RH strain, 4-6 weeks aged Swiss albino mice used in Sabin Feldman Dye Test applied in the Turkey Public Health Agency of Parasitology Laboratory are passaged routinely. Tachyzoites used to create T. gondii infection were obtained from the peritoneum of experimentally infected mice. The number of parasites in the tachyzoite suspension from mice was counted in the light microscope using the Neubauer Hemocytometer chamber. The infection was administered intraperitoneally to $1x10^4$ tachyzoites per millilitres. After three months of infection, it becomes chronic.

3.4. Behavioral Tests

- **Open Field Test:** This behavioral test setup, it is a square form made of plexiglass with dimensions of 100x100x30 cm. The test animal is gently placed in the center of the assembly. During the five-minute test, parameters such as the time spent at the center and edges, mobility time and speed are measured(Russo and Nestler, 2013).
- **Elevated Plus Maze Test:** In order to create anxiety, it is a device consisting of 4 arms which is 50 cm above the ground, two of which are closed and the other two are open. Two of the arms are closed by a wall with a height of 40 centimeters, while the other two are surrounded by 1 centimeters high plexiglas. Test animals placed in the center of the platform are subjected to testing for five minutes. Parameters such as the time spent in open and closed arms, the number of entries to open and closed arms, mobility time and speed are measured (Guimarães, Asth, et al., 2015).
- **Forced Swimming Test:** The platform is used in depression tests. It is a cylindrical platform with a diameter of 30 cm and a height of 50cm. It is filled with water at 28 degrees. The subject is released into the water. During the 5-min test, the

parameters such as total distance traveled, mobility time and speed are determined(Guimarães, Asth, et al., 2015)

- **Morris Water Maze Test:** Platform is a round pool filled water with a diameter of 180cm and a depth of 60cm. A hidden platform with a diameter of 10cm will be placed into the pool. The platform is fixed in the middle of one of the quadrans to be 1-2cm below the water. The temperature of the water is set to 23 ± 1°C. Colored geometric shaped tips are hanged on the walls of the room where the test is performed, so that the animal can see through the water.

The Moris water tank is divided into four regions: north, south, east and west. At 10-minute intervals, 4 times a day for 4 days, the learning trials are performed, the subject is taken to the testing phase on the 5th day. Animals are dropped from a different pole every day and the time to reach the platform is determined. (acquisition learning, learning trial). The animal released into the water is given 2 minutes to find the platform. If it cannot find the platform during this time, the animal is directed to the platform, gently placed on the platform and allowed to recognize it for 30 seconds. In the test phase, the platform is lifted and the parameters such as time spent in the platformquadrant is evaluated separately in 30 and 60 seconds slices (retention time: probe trial)(Kaur, Jindal, et al., 2013).

4. RESULTS AND DISCUSSION

4.1. Effects of Chronic T.Gondii Infection on Anxiety-like Behavior of F1 Generation of Infected Parent on the Open Field Test

When male or female groups studied, one-way analysis of variance (ANOVA) revealed significant main effects of infection, $F(2, 21)=4.36$, $p=0.03$. Figure 1 shows the total amount distanced travelled on Open Field Test. For the main effect of infection, post hoc comparisons showed that G1-F1 group male rats travelled less distance than those in the G2-F1 group. This means that the G1-F1 group male rats were more anxious than those in G2-F1 groups. However, there was no significant differences between female rat groups, $p>0.05$ (Figure 1). Compared to genders, one-way analysis of variance (ANOVA) revealed significant main effects of infection, for G1-F1 groups, $F(1, 14)=23.50$, $p=0.001$; for G2-F1 group $F(1, 14)=6.60$, $p=0.02$; for G4-F1 group, $F(1, 14)=9.38$, $p=0.008$. Female rats in all three groups travelled more distance than the male rats in all three groups. This means that the Female rats were less anxious than male rats in all groups.

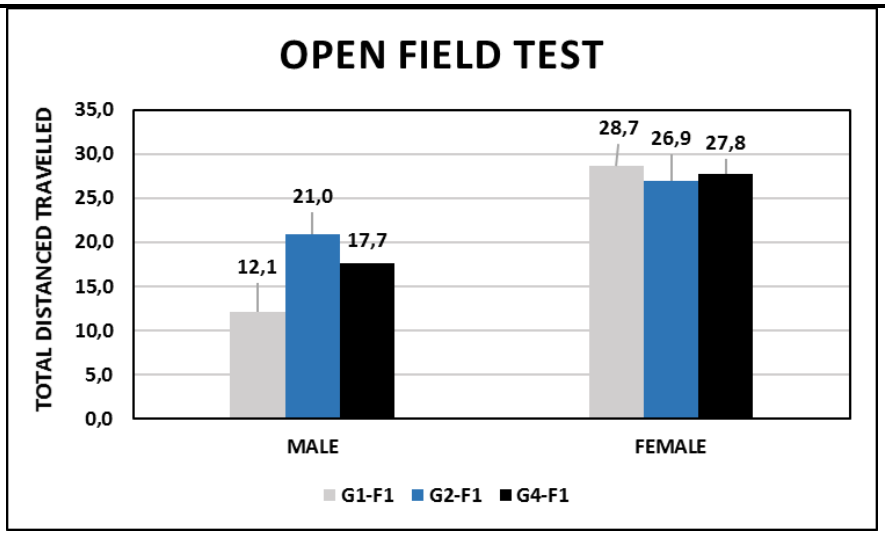

Figure 1. The total amount distanced travelled in open field test (TDT)

Moreover, Figure 2 shows average speed of rats in Open Field Test. There was a significant difference between G1-F1 and G2-F1 group male rats, $F(2, 21)=4.40$, $p=0.02$.G2-F1 group male rats was faster than G1-F1 group male rats. This means that the G1-F1 group male rats were more anxious than those in G2-F1 groups. However, there was no significant differences between female groups, $p>0.05$ (Figure 2). Compared to genders, there were significant differences between female and male rats in G1-F1, G2-F1 and G4-F1 groups, for G1-F1 groups, $F(1, 14)=23.75$, $p=0.001$; for G2-F1 group $F(1, 14)=6.66$, $p=0.02$; for G4-F1 group, $F(1, 14)=9.45$, $p=0.008$. Female rats in all three groups travelled more distance than the male rats in all three groups. This means that the female rats were less anxious than male rats in all groups.

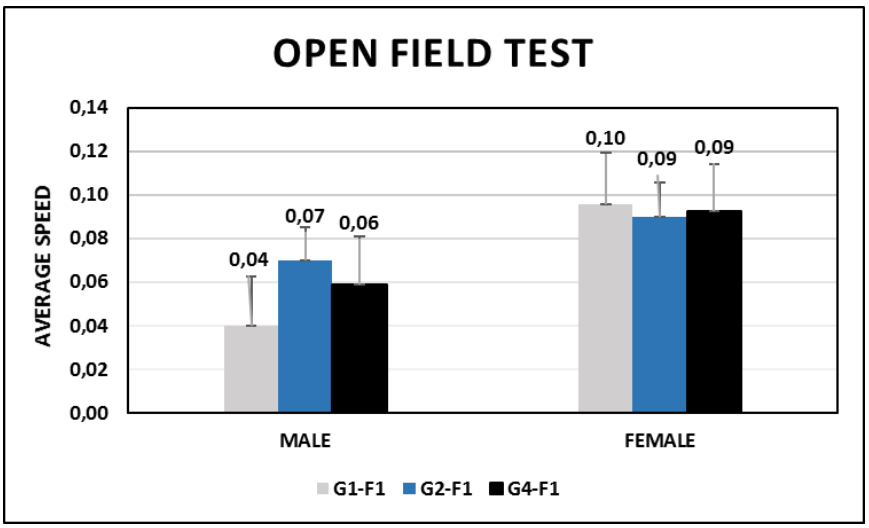

Figure 2. Average speed in open field test (AS)

4.2. Effects of Chronic T.Gondii Infection on Anxiety-like Behavior of F1 Generation of Infected Parent on the Elevated Plus Maze Test

Figure 3 shows time mobile of rats on Elevated Plus Maze Test. When all male groups studied, there was a significant difference between G1-F1 and G4-F1 and between G2-F1 and G4 F1, $F(2, 21)=7.29$, $p=0.004$. Post hoc analysis of the effect of infection indicated that G1-F1 and G2-F1 groups male rats were less mobile than G4-F1 group male rats. This means that the G1-F1 and G2-F1groups male rats were more anxious than those in G4-F1 groups. However, there were no significant differences between all female groups, $p>0.05$ (Figure 3). Compared to genders, there were no significant differences between female and male rats in G1-F1, G2-F1 and G4-F1 groups, $p>0.05$.

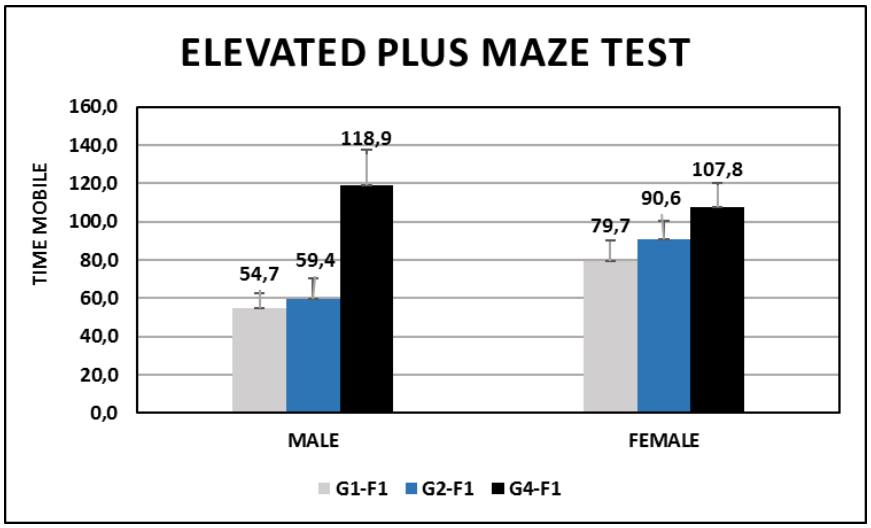

Figure 3. Time mobile on elevated plus maze test (TM)

When female groups studied, there was a significant difference between G1-F1 and G4-F1 groups female rats, $F(2, 21)=4.93$, $p=0.01$.G1-F1 group male rats were less frequently entered the open arm than G4-F1 group female rats (control). This means that the G4-F1 groups male rats were less anxious than those in G1-F1 group. However, there was no significant differences between all groups male rats, $p>0.05$ (Figure 4). Compared to genders, there were no significant differences between female and male rats in G1-F1, G2-F1 and G4-F1 groups, $p>0.05$.

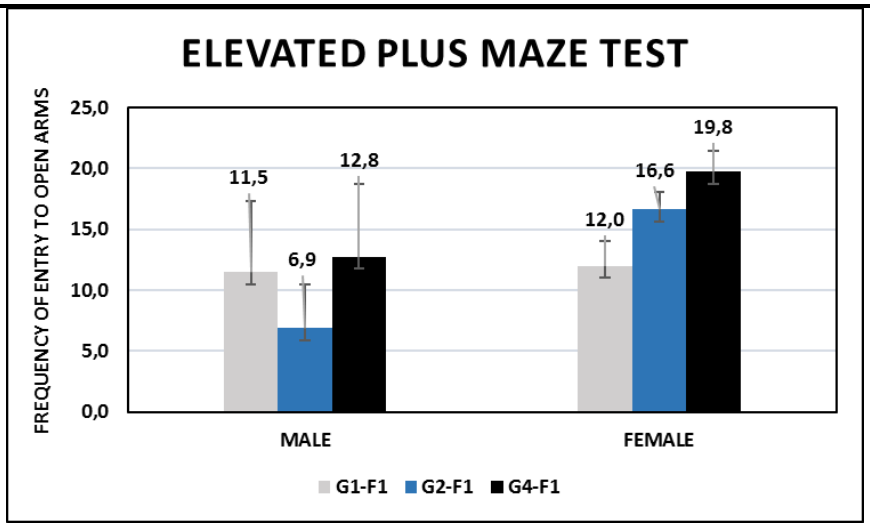

Figure 4. Frequency of Entry to Open Arms on Elevated Plus Maze Test (FEOA)

4.3. Effects of Chronic T.Gondii Infection on Depression-like Behavior of F1 Generation of Infected Parent on the Forced Swimming Test

Figure 5 shows total distance travelled of rats on Forced Swimming Test. When allgroups studied, there was a significant differences between G1-F1 and G4-F1 groups and between G2-F1 and G4-F1 groups female rats, $F(2,21)=7.55$, $p=0.003$. Post hoc analysis of the effect of infection indicated that G1-F1 and G2-F1 group female rats travelled more distance than those in the G4-F1 group female rats (control). This means that the G4-F1 groups female rats were less anxious than those in G1-F1 and G2-F1 groups. However, there was no significant differences between all male groups, $p>0.05$ (Figure 5). Compared to genders, there were significant differences between female and male rats in G2-F1, $F(1, 14)=33.18$, $p=0.001$. Female rats in G2-F1 groups travelled more distance than the male rats. This means that the female rats were less anxious than male rats.

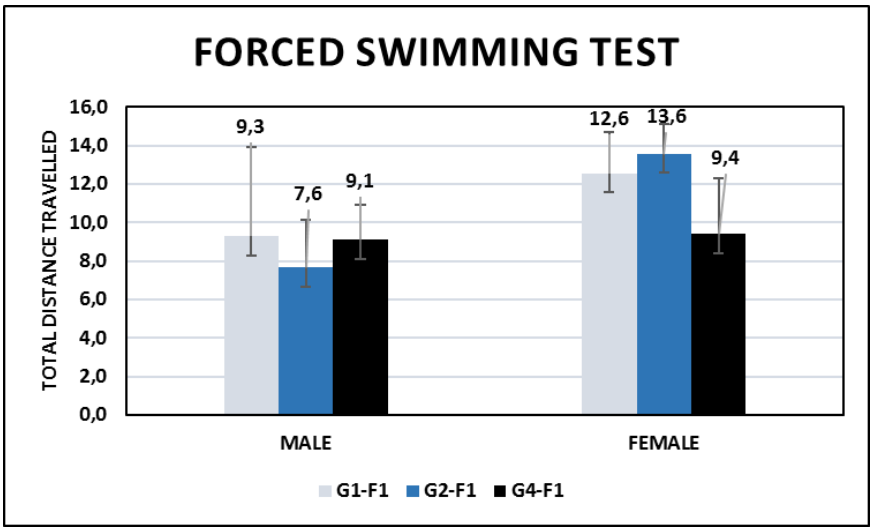

Figure 5. Total distanced travelled on forced swimming test (TDT)

Figure 6 shows max speed of rats on Forced Swimming Test. When all groups studied, there was a significant difference between G1-F1 and G2-F1 groups female rats, $F(2, 21)=3.45$, $p=0.04$.Max speed of G1-F1 group were more than G2-F1 female rats. However, there was no significant differences between all male groups, $F(1, 81)=2.05$, $p>0.05$ (Figure 6). Compared to genders, there were significant differences between female and male rats in G2-F1, $F(1, 14)=18.24$, $p=0.001$. Max speed of male rats in G2-F1 groups was more than the female rats.

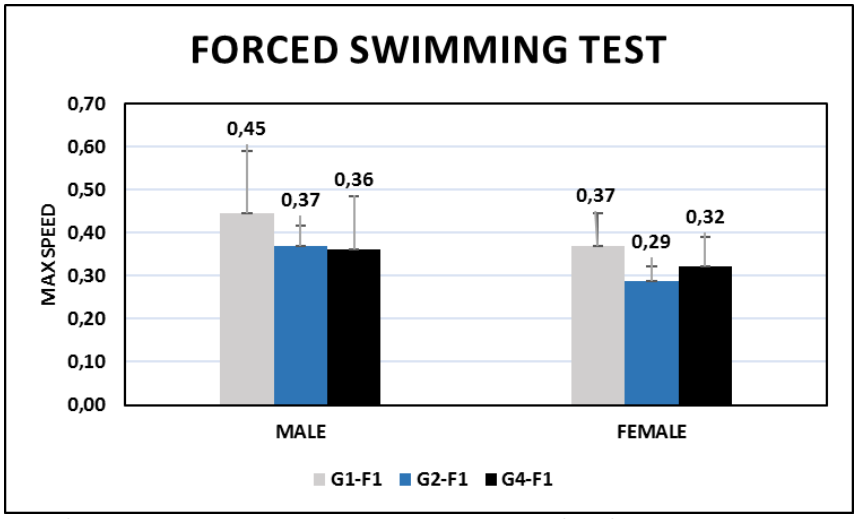

Figure 6. Max speed on forced swimming test (MS)

Figure 7 shows total distanced travelled on the surface of water on Forced Swimming Test. Analysis of the effects of T.Gondii infection on depression behavior of F1 generation rats demonstrated significant main effects of infection, $F(2, 21)=7.23$, $p=0.004$. G1-F1 and G2-F1 group female rats travelled more distance on the surface of the water than those in the G4-F1 group female rats (control). However, there was no significant differences between all male groups, $p>0.05$ (Figure 7). Compared to genders, there were significant differences between female and male rats in G2-F1, $F(1, 14)=32.15$, $p=0.001$. Total distanced travelled on the surface of water of female rats in G2-F1 groups were more than the male rats.

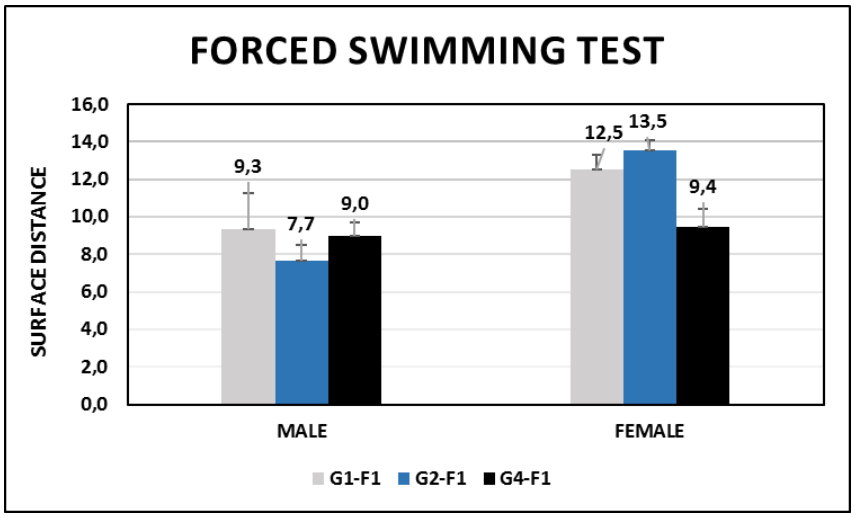

Figure 7. Surface distance on forced swimming test (SD)

Figure 8 shows that there was a significant differences between G1-F1 and G2-F1 groups and between G2-F1 and G4-F1 groups female rats, F(2, 21)=7.21, p=0.004. Post hoc analysis of the effect of infection showed that average speed on the surface of the water of G1-F1 group were more than those in the G4-F1 female rats and average speed on the surface of the water of G2-F1 group were more than those in the G4-F1 female rats. However, there was no significant differences between all male groups, F(1, 81)=2.05, p>0.16 (Figure 8).Compared to genders, there were significant differences between female and male rats in G2-F1, F(1, 14)=30.56, p=0.001. Average speed on the surface of water of female rats in G2-F1 groups were more than the male rats.

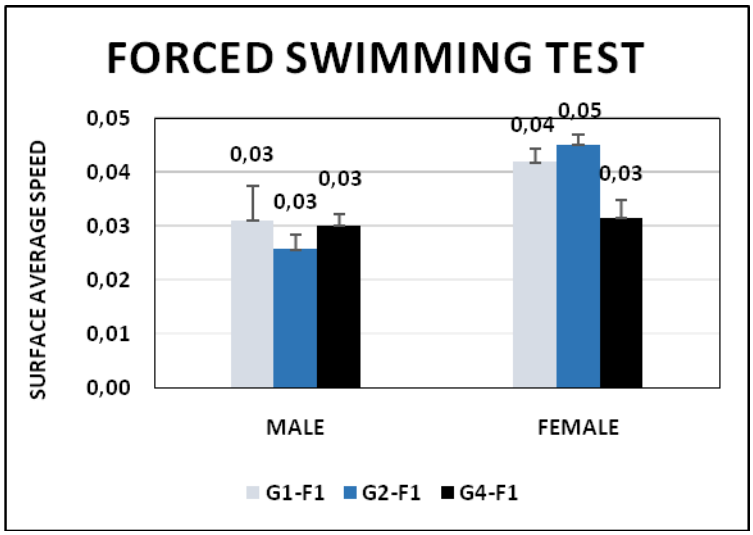

Figure 8. Surface average speed on forced swimming test (SAS)

4.4. Effects of chronic T.Gondi Infection on Depression-like Behavior of F1 Generation of Infected parent on Morris Water Maze Test

There was no significant differences between all groups.

4.5. Effects of Chronic T.Gondii Infection on Number of Offsprings of Infected Parent

Figure 9 shows number of offsprings of infected parent rats. According to this figure, there were significant differences between all groups. Number of offsprings of infected mother groups (G1) rats were less compared to non infected mother groups (G4 and G2. Especially, number of offsprings of infected both mother and father group (G3) were less compared to other groups. This result showed that offspring number of infected mother and father parental group more affected than those in infected mother or infected father parental groups.

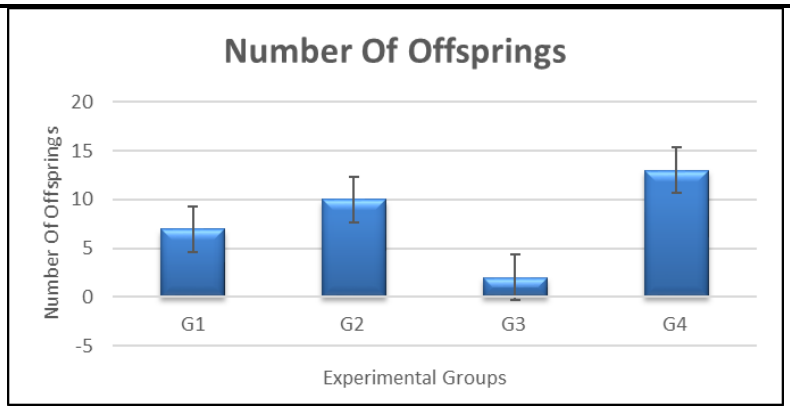

Figure 9. Number of offspring of infected parent rats

Table 1. Number of Offspring of Infected Parent Rats

Mean±Std.	Deviation
G1	7±1
G2	10±5
G3	2±2
G4	13±1

T.Gondii is a obligatory intracellular parasite that can be found in all cells of the body leading to significant diseases during the preterm period in the surviving newborn and spontaneous abortion that can pass the placental barrier. Studies have been conducted on extracted proteins of T.Gondii in order to better understand the molecular mechanisms that resulting to abnormalities on placental proteins and the results in pregnancy (Jiao, Zhang, et al., 2017). It has been found that 58 proteins were significantly upregulated or downregulated in the placenta of animals infected with T.Gondii. It has been found that fifteen of these proteins were associated with placenta development or trophoblast invasion. These proteins are mainly proteins that cause protease inhibitory activity, coagulation and acute phase responses and are involved in many biological processes. The disorder of these biological processes within the cell can affect the entire system, causing the cells to fail to function. It has also been reported that the disorders of these biological processes leads to growth retardation and pathological pregnancies resulting in fetal mortality(Dodson, Rozance, et al., 2013; Zubor, Kajo, et al., 2014; Duryea, Nicholson, et al., 2015). In our study, the number of offspring in groups of infected males and females was small compared to other groups, which may be due to changes made on placental proteins.

The effects of acute T.Gondii infection have been investigated, especially the effects on the fetus and the newborn during pregnancy have been reported. Although the effects of chronic T.Gondii infection have been investigated, it is not known yet. T.Gondii is an intracellular parasites. In the stage of acute and chronic infection, it may affect biological processes by causing changes in the amount of many proteins in host cells. Although T.Gondii infection is very common in the world, chronic infection is not treated in the clinic and it is thought to be ineffective in the latent period. Studies have shown that it causes change on placental proteins in the acute period and may affect many biological processes. These effects may cause different processes to occur until the chronic period. In addition, T.Gondii can be reactivated in the latent period due to any reason

that weakens the immune system of the host cell. In addition, it is very important to investigate the hormonal and immunogenic changes caused by infection in the host cells, which cause genetic and epigenetic causes in subsequent generations. T.Gondii is neurotrophic, it creates cysts in nerve cells in the long term and causes disruptions in the function of the region where it is located. For example, when it is located in amygdala, situations related to mood and especially fear are shaped(Misslin, 2003). Reactions such as attractiveness to cat odor have been reported in rats infected with T.Gondii (Vyas, Kim, et al., 2007). Although there is a neurotrophic parasite, there is no data on which region of the brain specifically prefers it. However, T.Gondii has been determined by hematoxylin eosin staining in which the density of tissue cysts was higher in amygdala region(Vyas, Kim, et al., 2007).T. gondii changes the behavior of the intermediate host when settled in specific brain regions.

In this study, in the 1st generation male offsprings of female rats with chronic T.Gondii infection, anxiety was increased in open area and locomotor activity was decreased. The mobility increased in the elevated maze test. In female offsprings, anxiety and depression are reduced. In parallel with the literature, T.Gondii infection was found to have different mechanisms in both males and females. Although it is not directly infected, it can be thought that it can be indirectly transmitted to female and male offspring from their mothers or fathers and that it can be seen in the offspring with different mechanisms. In a study conducted in humans, it was observed that T.Gondii increased taking risk in males, for example can lead to passing the red light, and infected women were more optimistic. In the results of our study, while the anxiety of male offspring is higher, the decrease of depression in female offspring is similar with this study. However, studies for the mechanism should be carried out.

Although prenatal infection may subsequently develop schizophrenia in the individual, but its mechanism is not known, it is thought that high maternal T.Gondii antibodies during pregnancy may be associated with schizophrenia in the offspring, although there is no significant effect on variable antibody levels(Brown, Landau, et al., 2011). The studies done in the last 60 years have proven to be susceptible to schizophrenia in individuals who have chronic, acute and maternal T.Gondii infection (Notarangelo, Wilson, et al., 2014; Chorlton, 2017). Schizophrenia is a world-wide disease with a complex and yet unknown pathogenesis caused by genetic environmental factors (Wigman, de Vos, et al., 2016). Since the 1950s, there is a hypothesis about the association of schizophrenia and T.Gondii infection (Buentello, 1958). In this study, it was shown that antibodies or proteins passing with maternal transfer, not direct infection agent, may have an effect on the behavior. However, the mechanism should be elucidated by molecular studies such as proteomics and genomics.

As a result, it has been observed that there are differences between female and male offspring same with the directly infected individuals. The effects of acute T.Gondii infection have been investigated in many studies. During pregnancy, it has been shown to have many effects from spontaneous abortion to mental illness in the early period, and this period has been seriously screened and followed by clinicians. In the chronic period, as in the acute period, it can be thought that proteins and antibodies are transferred by maternal or placental route. This study has strengthened the estimation that chronic infection can also be effective on offspring. In this study, a very small number of infants in the group of infected parents suggests

that T.Gondii infection can cause infertility or cause postpartum depression in females. In this study, it should be emphasized that there may be effects of antibodies or maternal proteins in chronic infection, not only in acute or reactive T.Gondii infection. Molecular level studies are needed to elucidate these mechanisms. Clinical awareness can be created by elucidation of the mechanism.

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NOTICE

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