The relationship between *Toxoplasma* infection in mothers and offspring gender

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Research article

Keywords: Toxoplasma infection, mothers, gender, sex ratio

Posted Date: February 3rd, 2020

DOI: https://doi.org/10.21203/rs.2.22470/v1

Abstract

Background:

Toxoplasma gondii is one of the most common parasitic protozoan in humans. It is a classical model for the study of manipulation hypothesis. The behavioral and hormonal changes, memory disorder, hyperactivity and even alterations in secondary sex ratio can be induced by manipulative activity of *Toxoplasma*. The secondary sex ratio may be influenced by many factors such as stress, immunosuppression and the age of parents. In this study, we evaluated the correlation between offspring gender and *Toxoplasma* infection in seropositive and seronegative mothers to *anti-Toxoplasma* IgG.

Methods:

From 2014 woman who had been tested for toxoplasmosis, the data of 137 mothers with chronic toxoplasmosis and 137 healthy counterparts were collected from clinics and hospitals of Shiraz, Iran.

The sex of the offspring, the mother's age, the number of girls and boys in previous pregnancies, the number and gender of abortions, contact with cats, food habits, education level, and residency were recorded for analysis.

Results:

The number of girls in *Toxoplasma*-seropositive and *Toxoplasma*-seronegative mothers was 165 (49.44%) and 136 (45.48%), respectively. Also, it was 163(54.51%) in the control group and 166(50.15%) in the seropositive group for male offsprings. there were significant sex ratio difference in the control group. No significant difference was observed for sex ratio of aborted fetuses between groups. However, in *Toxoplasma*-seropositive group, the sex ratio of aborted fetuses showed that the male aborted fetus were significantly higher in number.

Conclusion:

In this study, a significant relationship was found between chronic *Toxoplasma* infection and secondary sex ratio. However, it is suggested that this relationship be investigated in further studies as well as an animal study.

Background

Toxoplasma gondii is an obligate intracellular protozoan that causes toxoplasmosis. This zoonosis disease is a worldwide spread and prevalence of infection varies between 10–80% in various regions of the world [1, 2]. Infection occurs when the parasite is transmitted to humans by consuming foods like undercooked meat or drinks contaminated with oocysts or tissue cysts. Congenital transmission and organ transplantation are other routes of Toxoplasma infection [3].

Clinical manifestations associated with toxoplasmosis are very diverse. In immunocompromised patients, Toxoplasma causes acute toxoplasmosis due to the presence of tachyzoites in blood and other tissues and in immunocompetent individuals; it spontaneously turns into latent form. Latent toxoplasmosis is clinically asymptomatic but is characterized by the presence of anti-Toxoplasma antibodies in serum and Toxoplasma bradyzoites in tissue cysts [4, 5]. Once a pregnant woman is infected with this parasite, the possibility of congenital transmission is high and the clinical symptoms are different including abortion and serious manifestations such as hydrocephaly and microcephaly [6, 7].

Latent toxoplasmosis may increase the risk of psychiatric and neurological abnormalities and personality changes such as bipolar disorder, obsessive-compulsive disorder, recurrent migraine, cryptic epilepsy, autism and brain tumor [4, 8]. It can also affect human pregnancy and may change the rate of the secondary sex ratio (the ratio of males to females at birth) [9, 10].

The secondary sex ratio is around 0.51 in different human societies and some factors including age of parents, stress, immunosuppression, paternal endocrine disruption and socioeconomic status of the parents can affect it [10]. Since the diseases may influence the endocrine hormones and immune system, they may also affect sex ratio by immune response and cytokine production [11, 12]. Few studies have assessed the effects of latent Toxoplasma infection on sex ratio at birth in humans and mice [13–15], this study was designed to investigate the relationship between Toxoplasma infection of mothers and neonate gender

Methods

Patients and controls

The data of 2014 mothers were collected between 2015–2018 from individuals who were referred to Motahari clinic of shiraz, Iran, after approval by institutional ethics committee of Shiraz University of Medical Sciences (Ethical code: IR.SUMS.REC.1398.224) and written informed consent for their participation. This information belongs to mothers who had been tested for toxoplasma infection during their pregnancy; the mothers were divided into two groups based on their being seropositive and seronegative to anti-Toxoplasma IgG. In this study we excluded mothers who died for various reasons including cancer. The Information contained of mother’s age, previous deliveries and abortions, contact with cat, diet, location and Level of education.

Statistical analysis

Statistical analysis was performed using SPSS and Medcalc. Frequency distributions of the variables were compared among those with positive or negative Toxoplasma test results using Chi-square test. The logistic regression was used to evaluate the relationship between the sex ratio and anti-Toxoplasma antibodies titer values. Differences with P- values less than 0.05 were considered significant.

Results

The population study included 2014 mothers who were referred to Motahari Clinic in Shiraz during 2015–2018. The mothers had been tested for toxoplasma infection during their pregnancy, 326 mothers were IgG seropositive to Toxoplasma and 1688 were negative for IgG. The prevalence of Toxoplasma infection was 16.2% in the population of this study. The mean age of mothers was 34.21 (± 8.918) years.

The mothers were separated into two groups including 137 according to their being seropositive and seronegative to Toxoplasma. The age distributions were also similar, with a mean age of 34.3 ± 9.077 years in seropositive mothers and 34.12 ± 8.789 years in seronegative mother. The difference was not statistically significant (p = 0.443). (Table 1)

Table 1
Distribution of age index in seronegative and seropositive mothers groups

Age of	mean	min	max	Standard deviation
Seropositive mothers	34.3	18	69	9.077
Seronegative mother	34.12	19	67	8.789
Total	34.21	18	69	8.918

Toxoplasma-seropositive mothers who had more contact with cat were significantly higher compared to the control group (26 vs. 5, p = 0.001), significant differences were also seen between seropositivity to toxoplasma infection and diet (p < 0.001).

The Education and place of residence was not statistically significant difference between T. gondii-seropositive and seronegative mothers (p = 0.5, p = 0.464 respectively).

We compared the gender of springs between the toxoplasma-seropositive and toxoplasma-seronegative (control) groups. The female offspring was 136 (45.48%) and 165 (49.84%) in the control and seropositive group respectively. Also, it was 163 (54.51%) in the control group and 166 (50.15%) in the seropositive group for male offspring (Table 2). No significant differences were observed for the sex ratio between groups and in seropositive mothers to toxoplasma but there were significant sex ratio difference in the control group. The percentage of male offsprings was higher in this group. (54.5%, p = 0.015)

Table 2
prevalence of male and female offsprings in seropositive and seronegative mothers

Sex	Seronegative mothers		Seropositive mothers	
	percentage	number	percentage	number
Male offspring	54.51%	163	50.15%	166
Female offspring	45.48%	136	49.84%	165

The number of abortion in the seropositive group was 44, including 31(70.45%) male and 13 (29.54%) female fetus. While from the total of 37 abortions in the seronegative group, 19 (51.35%) were female and 18 (48.64%) were male (Table 3). The differences in the sex ratio of abortions were not significant between groups and in the control group. But sex ratio of aborted fetuses showed that significant difference in the seropositive group. The percentage of male aborted fetus was higher in this group. (31, $p < 0.001$)

Table 3
Prevalence of aborted fetuses in seropositive and seronegative mothers by gender

sex	Seropositive mothers		Seronegative mothers	
	percentage	number	percentage	number
Male fetus	70.45%	31	48.64%	18
Female fetus	29.54%	13	51.35%	19

Discussion

The results of this study showed that there was a relationship between the latent Toxoplasmosis and the secondary sex ratio such that the secondary sex ratio in Toxoplasma seronegative mothers was significantly higher than in those with seropositive toxoplasmosis. Mothers with seropositive history to Toxoplasma had more female offsprings. Also, the study showed that there is a significant association between the gender of abortions and toxoplasmosis, such that Toxoplasma-seropositive mothers had higher rates of male abortion.

Previously, the relationship between Toxoplasma gondii and secondary sex ratio has been studied. Dama et al., in 2016[13], examined the possible relationship between Toxoplasma gondii and secondary sex ratio. Their findings showed that mothers with latent toxoplasmosis tend to give birth to more boys than girls. Also, in a retrospective cohort study in 2007, Kaňková et al., [14] showed that higher anti-Toxoplasma antibody concentrations increased the probability of giving birth to a boy to 0.72. They

speculate that the effect of Toxoplasma on suppression or modulation of the immune system could lead to the survival of more male fetuses. In another study, Shojaee et al., [15] indicated that T. gondii infection affects secondary sex ratio in human offspring and can be addressed as one of the main causes of abortion in women. The results of the above studies are in conflict with the present study. This suggests that further research in different populations is needed to prove this hypothesis because the secondary sex ratio may be influenced by other factors in addition to toxoplasmosis such as the age of the mother, the sex of preceding siblings, immune status and other diseases [10, 12, 16, 17].

In an animal study, the researchers found that in the late phase of toxoplasmosis, mice produce more female offsprings although in the early phase of Toxoplasma infection, mice produce more male offsprings. [18]. The results of this study, similar to our study, show that the chances of a girl born are higher in mothers with chronic toxoplasmosis. This difference may be due to higher rates of male abortions in mothers with chronic toxoplasmosis, which is also reported in the present study.

The prevalence of anti-Toxoplasma IgG antibody was 16.2% in the present study, and it was significantly associated with the exposure to cats and diet. According to a study by Shaddel et al., in Shiraz,[19] the prevalence of anti-Toxoplasma IgG was 23.2% in blood donors. The cause of this disagreement can be attributed to gender imbalance in the population of blood donors most of which are men. They found that the prevalence of chronic toxoplasmosis was higher in people with low education. However, in our study, no significant relationship was found between the seropositive and seronegative groups in terms of level of education.

Fallah et al., [20] in 576 women at Gravid Primates found that consumption of raw meat and vegetables was significantly associated with the prevalence of Toxoplasmosis. We also found a significant association between eating habits, including raw and half-cooked meat, and toxoplasma antibody levels. But in this study there was no relationship between exposure to cats and the prevalence of anti-Toxoplasma antibody, while in the present study we found a significant relationship with $P < 0.001$.

Also, in the study of Olariu et al., the prevalence of Toxoplasma gondii antibodies in women in Romania was 57.6% and rose with increasing age [21]. In our study, the prevalence of Toxoplasma was 16.2%. The age of the population in our study had a lower mean age than the population in the study of Olariu et al. Moreover, low rate of Toxoplasma infection prevalence among our study may be due to the random selection of younger individual in this study compared to other investigations.

This study showed that abortion rates were also higher in mothers with chronic toxoplasmosis, but no association was found between abortion and the prevalence of toxoplasmosis. By Asgari et al., In 2013[22], the prevalence of Toxoplasma in spontaneous abortion samples in Shiraz was reported 14.4%, and Toxoplasma infection was recognized as a risk factor for abortion. This difference is probably due to in the sensitivity of used methods as the molecular methods used in this study is more sensitive than the serological methods used in our study.

Conclusion

In this study, a relationship was found between chronic Toxoplasma infection and secondary sex ratio. However, it is suggested that this relationship be prospectively investigated in future studies to follow up the sex of offspring. Future research my also include studies on laboratory animals to obtain more reliable results.

Abbreviations

IgG: Immunoglobulin G; SPSS: Statistical package for the social sciences

Declarations

Ethics approval and consent to participate

The current study was approved by the Ethical Committee of Shiraz University of Medical Sciences, Shiraz, Iran (Ethical code: IR.SUMS.REC.1398.224). Informed written consent was obtained from all participants before being involved in the study. All participants signed an informed consent and received a complete copy of the signed consent form.

Consent for publication

Not applicable.

Availability of data and materials

The dataset used and/or analyzed during the current study is available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

The study was financially supported by the office of vice-chancellor for research of Shiraz University of Medical Sciences (Grant No. 19664)

Authors' contributions

QA coordinated in designing the project and providing financial supports. FZ, MSB, ND and PP gathered the information of mothers and MSB analyzed the data. MSB, ND and PP carried out drafted the original manuscript and all authors read and approved the final version of the manuscript.

Acknowledgements

This study was undertaken as an MD degree thesis for Fatemeh Zarei. The author’s thanks from hospitals and clinics for their solidarity.

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