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Original Research

Prevalence of *Toxoplasma gondii* During Pregnancy and the Function of the IL6-174 G>C Mutation

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Abstract

Toxoplasma gondii is an intracellular parasite that leads to congenital toxoplasmosis and to neuro-ocular sequelae in newborns, some of which are severe, stillbirth and miscarriage. Polymorphisms in cytokine genes is one factor of the host genome that might be involved in the susceptibility to infection during prenatal period. In this study, the susceptibility of pregnant women to *Toxoplasma gondii* infection was investigated in relation to IL6 174 G>C (rs1800795) polymorphism.

Methods: The Women's and Children's Hospital in Babylon, Iraq, undertook a case control study from November 2024 to February 2024. Fifty pregnant women were included in the study; 20 of them were cases with proven *T. gondii* infection (anti IgG positive) and 30 were healthy controls who tested negative for the parasite. Allele Specific PCR for the IL6 174 G>C polymorphism was used for genotyping. A computerised VIDAS Toxo IgG II (ELFA) developed by bioMérieux in France was used to screen the sera for anti-*T. gondii* IgG antibodies. Logistic regression was used for estimation of odds ratio (OR) under the codominant, dominant and recessive genetic model, and Fisher's exact test was used to compare the frequencies of geno/alleles.

Results: In the cases, the GC heterozygote was significantly more common (50%) than in the controls (16.7%). There was a significant in the overall genotype distribution between the two groups (Fisher's exact test; P = 0.041). Under the codominant model, with GG as the reference, logistic regression analysis showed association of the GC genotype with an increased risk of infection (OR = 5.667, 95% CI: 1.369–23.462, P = 0.017). The model with overdominant high risk for heterozygotes (GC vs. GG+CC) was confirmed with strong and statistically significant increased risk (OR = 5.000, 95% CI: 1.363–18.348, P = 0.015). There was no significant found between the CC

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homozygote (OR = 1.417, P = 0.653). The control group was not in Hardy Weinberg equilibrium ($\chi^2 = 12.05$, df = 1, P < 0.001), which was due to the small sample size.

Conclusion: The IL6 174 G>C polymorphism and specially the heterozygote GC is more susceptible to the *Toxoplasma gondii* during pregnancy. This could be due to an over-dominant effect, in which one copy of the C allele changes the regulation of interleukin 6, which could upset the Th1/Th2 balance that is necessary for parasite control and foetal immune tolerance. Prior to clinical translation, bigger multicenter prospective trials with direct measurement of blood IL 6 levels are necessary to assess the polymorphism's potential as a genetic marker for risk stratification in prenatal treatment.

Keywords: *Toxoplasma gondii*, IL6 polymorphism, congenital infection, Iraqi population.

Introduction

Toxoplasmosis, which is brought on by the obligatory intracellular polyphagan parasite about one-third of the world's population is infected with *Toxoplasma gondii*, making it one of the most common zoonotic illnesses [1]. Although, in immunocompetent individuals, the infection often produces cold-like symptoms and is self-limited or asymptomatic, a serious health threat during pregnancy is the infection [2]. Congenital *Toxoplasma gondii* infection can result from a primary infection in the mother and the passage of the infection vertically through the placenta. Hydrocephalus, microcephaly, intracranial calcifications, and chorioretinitis are some of the serious neurological and ocular sequelae that might affect the foetus, and they can appear at birth or later in life [3,4]. The severity of foetal damage is worst when the infection occurs in the early stages of pregnancy, but the risk of transplacental transmission increases from 15% in the 1st trimester to > 70% in the 3rd trimester [5,6].

The viability of the placenta and foetal infection with *Toxoplasma gondii* will be largely determined by the balance between the immune response of the mother at the feto-maternal interface [7]. A shift from a pro-inflammatory (Th1) to anti-inflammatory (Th2) immune response is necessary to promote immune tolerance towards the partially allogeneic foetus and must happen during pregnancy [8]. Th1 cytokines ((TNF α), (IFN γ) and (IL 2)) are generally associated with pregnancy loss while Th2 cytokines (like interleukin 4 (IL 4), IL 5, IL 10, and IL 6) are associated with fetal protection. The immunological challenge is that while a strong Th1 mediated cellular immune response is required for the successful clearance of intracellular pathogens such as Toxoplasma gondii, an excessive Th1 response or a response that persists too long can disrupt the tolerant environment that is required for the survival of the foetus [11,12].

One of the cytokines involved in this complex balance is interleukin 6 (IL6) that has a dual role [13]. IL 6, a pleiotropic cytokine, plays a role in pro- and anti-inflammatory pathways [14]. Increased levels of maternal serum and amniotic fluid IL 6 have been associated with poor pregnancy outcomes such as preterm labor, intrauterine infection, and spontaneous abortion [15,16] due to the systemic and local elevation of IL 6 levels following a *Toxoplasma gondii* infection. Moreover, a recent meta-analysis and thorough review [17] has shown that polymorphisms of IL 6 are involved in the significantly altered interleukin profiles of women. We still don't fully understand how IL 6 controls the risk of congenital toxoplasmosis, though [18].

The genetic polymorphisms in the IL6 promoter region have been implicated in affecting transcriptional activity and cytokine production [19]. One of these, the SNP at position -174 (G>C, rs1800795), has been studied extensively in connection with various inflammatory and infectious diseases [20]. The change in IL-6 expression is due to its effect on the binding ability of transcription factors such as NF-1 and Smad4 [21,22]. Some studies have revealed that relative to GG wild type genotype, the IL 6 level

is elevated in GC heterozygote and CC homozygote [23]. In Middle Eastern cultures, where toxoplasmosis is still rather common, the link between this particular SNP and pregnancy-related T. gondii infection has not been thoroughly studied [24].

Thus, this study aimed to answer the following questions: (i) to compare the total number of pregnant women who were diagnosed with Toxoplasmosis to healthy pregnant in Babylon, Iraq; (ii) to determine the prevalence of the three different genotypes of this SNP (GG, GC, and CC) in the two groups; and (iii) to evaluate if a specific genotype or allele of this SNP is associated with higher risk for Toxoplasmosis in pregnant. The results may assist in the identification of high-risk pregnant women for congenital toxoplasmosis, which may enable targeted prevention and prenatal care for these women [25]. They will also provide insights into host genetic determinants of susceptibility to this condition.

Materials and Methods

The study of methodology and subjects involved in research.

Babylon, Iraq's Women's and Children's Hospital was the site of this case-control research, which ran from November 2024 through February 2024. Twenty of the fifty pregnant studied were identified as being infected with *T. gondii* (anti-T. gondii IgG antibodies were positive), thirty were judged to be healthy and had negative anti-T. gondii serology results. During their first prenatal appointment, all participants were enlisted. Those who had a history of immunodeficiency, chronic inflammatory diseases, multiple pregnancies, or chronic or acute infections were not selected [26,27].

Collecting blood and doing serological tests

Venous blood (5 mL) was collected from all subjects by standard venipuncture. The separated serum was stored at 4°C until analysed after having been centrifuged for 10 minutes at 3000 rpm. The automated VIDAS Toxo IgG II (ELFA) was used for serological screening of anti-T. gondii IgG antibodies in accordance with the manufacturer's instructions. Based on the aforementioned cut off values, the assay results were classified as positive, negative or inconclusive [5,6].

DNA Isolation

The blood sample from the umbilical cord was used in the DNA extraction process and a High Pure PCR Template Kit was used. The DNA was mixed with 100 µL of elution buffer after extraction and kept at -20 °C until it was time for molecular analysis [28,29].

The IL6 –174 G>C (rs1800795) polymorphism was genotyped.

The Allele Specific polymerase chain reaction system (AS-PCR) was used to genotype the single nucleotide polymorphism (SNP) IL6 -174 G>C. Refer to Table 1 for all the primer sequence, amplicon length and annealing temperature details [30,31].

Table 1. Primers used for nested PCR amplification of the IL6 –184 G>C region.

Gene	SNP name	Primer sequences (5′–3′)	Annealing temperature (°C)	Amplicon length (bp)
IL-6	IL6–174 G>C SNPs	IL6 R:GAGCTTCTCTTTCGTTCC	52	543
		IL6C:CCCTAGTTGTGCTTGCC		
		IL6G: CCCTAGTTGTGCTTGCG		

A HotStarTaq® Master Mix Kit was used to conduct the amplifications by the German company Quantigen. The polymerase chain reaction (PCR) program started with 15 minutes

activation at 95°C followed by 40 denaturation cycles of (30 seconds denaturation, 1 minute annealing, 2 minutes extension and 10 minutes final extension at 72°C). A 543 bp band size was generated by the PCR. The 10 µl of AS-PCR was loaded on a 2 % agarose gel that was stained with ethidium bromide and the gel was illuminated using UV light [32,33]. When one set of bands from an allele appears and the other set disappears, we say that the person is GG wild type homozygous [34,35]. On the other hand, when one set of bands from an allele appears and the other sets disappears, we say that they are CC mutant type homozygous [34,35].

Analysis of data with statistical tools

Descriptive statistics were used in the determination of both sets of genotypes and allele frequencies. Since the number of cells was expected to be small, Fisher's exact test (two-sided) was used to compare the frequencies of the genotypes among patients and controls. The relationship between each genotype and the presence of T. gondii was determined with binary logistic regression. The reference (codominant model) was the GG genotype and 95% confidence intervals (CIs) were estimated. Additionally, we have compared GG to recessive CC and GG+GC models, as well as GC to GG+CC, and dominant GC+CC vs. GG. A statistically significant result was defined as $P < 0.05$ and all statistical tests were two-sided. A chi-square goodness-of-fit test, with one degree of freedom, was performed to see whether the control group was in Hardy-Weinberg equilibrium (HWE). We used IBM SPSS Statistics, version 26.0 to conduct our statistical analyses [36,37].

Study of genotyping and the population, results

Fifty pregnant women were included in the study; 20 of these women were in the "case group" and had a proven infection of Toxoplasma gondii, while 30 of these women were in the "control group" and healthy. The genotyping of the IL6 -174 G>C polymorphism (rs1800795) was performed in all the subjects. An recognised weakness of the study is that the genotype distribution in the control group did not follow the Hardy-Weinberg equilibrium ($\chi^2 = 12.05$, df = 1, $P < 0.001$). This deviation may be caused by sample size and/or population substructure.

Different variations of genes and their prevalence.

In the case group, 30% (6/20), 50% (10/20), and 20% (4/20) of the participants had the GG, GC, and CC genotypes, respectively. These percentages were 57.6% (17/30), 16.7% (5/30), and 26.7% (8/30) in the control group, respectively. The GC genotype was much more common in the infected women than in controls (50 percent vs. 16.7 percent).

A variety of genetic models for association analysis

There was a statistically significant difference ($P = 0.041$) when we first evaluated the total distribution of genotypes between patients and controls using Fisher's exact test. Each genotype was then scored for risk, using binary logistic regression with the GG genotype as the reference (codominant model). The odds ratio (OR) for the GC heterozygote and CC homozygote were 5.667 (95% confidence interval [CI] = 1.369-23.462, $P = 0.017$) and 1.417 (95% CI = 0.310-6.470, $P = 0.653$), respectively, indicating that the GC heterozygote is significantly more likely to have a Toxoplasma gondii infection.

We examined the dominant-recessive model and overdominant model to gain more understanding of the inheritance mode. A non-significant trend was shown by the OR of 3.051 (95% CI = 0.921-10.114, $P = 0.068$) in the dominant model (GC+CC vs. GG). The recessive model (CC vs. GG+GC) did not reveal any association with a 95% confidence interval (CI) of 0.176 to 2.687 and a p-value of 0.590. Specifically, there was a high and statistically significant increased risk of heterozygotes for the overdominant model (GC vs. GG+CC) (OR = 5.000, 95% CI = 1.363-18.348, $P = 0.015$).

All logistic regressions were adjusted for the appropriate genetic contrast. Summary of the main findings is given in Table 2.

Table 2. Association of the IL6 −174 G>C polymorphism with Toxoplasma gondii infection under different genetic models.

Genetic model	Genotype comparison	Cases (n=20)	Controls (n=30)	OR (95% CI)	*P* value*
Codominant	GG (ref)	6 (30%)	17 (56.7%)	1.00	–
	GC	10 (50%)	5 (16.7%)	5.667 (1.369–23.462)	**0.017**
	CC	4 (20%)	8 (26.7%)	1.417 (0.310–6.470)	0.653
Dominant	GG (ref)	6 (30%)	17 (56.7%)	1.00	–
	GC+CC	14 (70%)	13 (43.3%)	3.051 (0.921–10.114)	0.068
Recessive	GG+GC (ref)	16 (80%)	22 (73.3%)	1.00	–
	CC	4 (20%)	8 (26.7%)	0.688 (0.176–2.687)	0.590
Over-dominant	GG+CC (ref)	10 (50%)	25 (83.3%)	1.00	–
	GC	10 (50%)	5 (16.7%)	5.000 (1.363–18.348)	**0.015**

*P values were obtained from binary logistic regression. Statistically significant associations ($P < 0.05$) are indicated in bold.

Discussion

1. Important findings and understanding genetic models.

The current research is the first to indicate that pregnant Iraqi women with the IL6 -174 G>C (rs1800795) genotype are more likely to contract Toxoplasma gondii. A 5.67-fold greater risk was related with the heterozygous GC genotype under the codominant model (OR = 5.67, 95% CI: 1.37-23.46, P = 0.017). Under the overdominant model, this effect was confirmed (GC vs. GG+CC: OR = 5.00, 95% CI: 1.36-18.35, P = 0.015). There was no correlation observed in the CC homozygote. This preponderance pattern suggests that people with one C allele produce IL 6 in such a way that they are more susceptible, and people with two C alleles might be less vulnerable. This advantage or disadvantage is not limited to infectious disorders; other cytokine polymorphisms have been described as having such an advantage or disadvantage for heterozygotes [38,39].

In a previous study on congenital toxoplasmosis, Wujcicka et al. [40] found that the GC genotype at the IL6 -174 G>C SNP (corresponding to the same rs1800795 SNP) was highly associated with the disease, with an odds ratio (OR) equal to 4.24 (95% CI: 1.24-14.50) in the codominant mode of inheritance and that the C alleles were significantly more prevalent among congenital toxoplasmosis patients than among non-toxoplasmosis patients. Our results are very similar to this earlier study with regard to the size of the odds ratio (5.667 vs. 4.24) and the heterozygote effect. This agreement is very convincing proof of the reality of the rs1800795 (GC) genotype as a risk factor in the biological world for congenital toxoplasmosis.

2. The toxoplasmosis in pregnancy burden on a global scale

1/3 of the world's population is infected with T. gondii. With a median value of 35.64% and high heterogeneity (I^2 = 99.61%), a 2023 comprehensive review and meta-analysis

comprising 29,383 pregnant women from the WHO Eastern Mediterranean region revealed a pooled seroprevalence of 36.5% (95% CI: 32.6-40.4) [1]. A recent meta-analysis (1994–2023) showed that overall, 27.5% of Saudis had toxoplasmosis (28% of the pregnant women) (2). In accordance with the heavy public health problem in this area, studies have revealed rates of seroprevalence of 30-45% in pregnant women in Iraq [41,42]. These numbers highlight the importance of finding host genetic indicators to enable preventive efforts reach women at high risk.

3. The importance of rs1800795 in a functional context and its impact on certain pathogens

Located in the IL6 promoter, the rs1800795 (-174 G>C) polymorphism changes the binding sites for transcription factors including NF 1 and Smad4, which in turn affects the activity of transcription. Interestingly, researchers determined that the minor allele (C) of the rs1800795 was associated with significantly higher expression of IL 6, which they suggested represented a transcriptional rather than post-transcriptional control mechanism [43]. Genotype with high expression of IL 6 has been associated with the presence of high levels of IL 6 in a number of inflammatory disorders [44]. Nonetheless, there is a remarkable variation in the direction of correlation with infection risk among pathogens. For example, the IL6 rs1800795 C allele was associated with severe sepsis and septic shock in community-acquired pneumonia (CAP) patients [45]. A 2024 meta-analysis of 58 studies and 13,696 patients revealed that genetic polymorphisms in IL 1β (-511T>C), IL 6 (-174 G>C), and IL 10 are significantly associated with RPL. Ethnic subgroup analysis also showed that these differences were strongly associated with RPL risk in the Asian population [17]. The impact of IL6 rs1800795, then, is situational. As suggested in the theory that an exaggerated IL-6 response at the maternal/fetal interface can disrupt the balance required to control the parasite without compromising pregnancy [46,47], our results indicate that the GC genotype is more susceptible to T. gondii.

4. The immunological conflict during pregnancy - Th1/Th2 balance

In order to have a successful pregnancy, a shift from the inflammatory Th1 to the anti-inflammatory Th2 profile is required. Excessive production of Th1 cytokines (such as TNF α and IFN γ) can typically be responsible for abortions, while the production of Th2 cytokines (such as IL 4, IL 5, IL 10 and IL 6) help to induce foetal tolerance [48]. Still, a strong Th1 response is necessary for T. gondii management, an intracellular parasite. This makes for a subtextual disagreement. Prior research on pregnant mice infected with Toxoplasma gondii has shown that the immune responses of the placentas, lungs, and spleens were mostly characterised by IFN γ and TNF α, rather than IL 6 or IL 4. Conversely, the imbalance of IL 6 and TNF levels along with FOXP3 expression at feto-maternal interface has been associated with bad pregnancy outcomes [51,52]. Our genetic information suggests that the GC genotype may be linked to an increase in the inflammatory response to IL 6, and therefore to a state of inflammation that would facilitate infections and would make pregnancy maintenance more difficult.

5. The acknowledgeable restriction of the Hardy-Weinberg equilibrium

The control group had a significant deviation from Hardy Weinberg equilibrium ($\chi^2 = 12.05$, df = 1, $P < 0.001$). This may be due to the limited number of patients (n = 30), consanguinity which was common among the patients studied, or selection bias inherent in a hospital population. As recommended by STREGA [53] a significant difference in HEWs between controls and cases should be documented and discussed, but not necessarily invalidate a case control association. We agree that it is a disadvantage, and have stressed the need for larger scale, population-based replications.

6. Research related to IL6 and toxoplasmosis reviewed.

Our results are similar to those of Wujcicka et al. (2015) [40] who analyzed 22 foetuses/neonates

with congenital toxoplasmosis and 49 controls for the polymorphisms IL6 -174 G>C and IL1B +3954 C>T, using a comparable nested PCR RFLP methodology. The study found that having the C allele at the IL6 -174 G>C SNP was more common in infected cases compared to uninfected ones, and that being GC heterozygotes at this SNP was significantly linked to toxoplasmosis. Its remarkable that, if I compare our results (OR = 5.667) with those of Wujcicka et al. (OR = 4.24) the results are similar for both populations (Polish vs. Iraqi) and both types of samples (newborns/fetuses vs. pregnant women). The convergence seems to be strong, across ethnic subgroups and appears to validate the involvement of the IL6 rs1800795 in congenital toxoplasmosis susceptibility.

7. Advantages and disadvantages

In conclusion, this study is an important one, as it is the first to examine the IL6 -174 G>C polymorphism in relation to T. gondii infection in pregnant women of Iraq. We applied codominant and overdominant models to see that we were able to detect a specific heterozygote effect which would not have been seen in the simple allelic analysis. We used the standardised VIDAS ELFA for serological diagnosis and strict nested PCR RFLP for genotyping in order to ensure the reproducibility of our results. Furthermore, our observed association is also supported by biological plausibility because of similarity of our results to the previous Polish study.

Limitations: Wide confidence intervals were a consequence of the small sample size (20 cases and 30 controls), which reduces statistical power. The single center concept may not be suitable for other populations in the Middle East or from Iraq. We were not able to make direct measurements of serum IL 6 levels, so the relationship between genotype and protein expression is inferred. The risk of T. gondii infection is known to be influenced by exposure to cats, raw meat diet and hygiene [54,55] but these were not multivariate adjusted. It should be noted that the control group is not in Hardy-Weinberg equilibrium, and this needs to be interpreted carefully. In order to validate our findings, more large-scale and multi-center prospective studies need to be conducted to directly measure cytokines and to include all environmental risk variables.

Conclusion

We found that pregnant women with the IL6 -174 G>C polymorphism (particularly the heterozygote genotype GC) have a risk of five times acquiring a Toxoplasma gondii infection. This finding confirms the strong cross-population effect, which is in good agreement with the previous Polish study done by Wujcicka et al. [40]. The preponderance pattern is in which only one copy of the C allele alters the regulation of IL 6, making one more susceptible. If this is confirmed in larger, independent patient groups, from different ethnicities, then screening may have the potential to identify women who may be at greater risk of developing this variant and may benefit from targeted preventive counselling and closer serological monitoring during pregnancy. It is important to have larger sample sizes, multivariate adjustment and direct measurement of serum IL 6 levels in future studies to confirm the clinical utility of the genetic marker rs1800795 as a susceptibility marker for toxoplasmosis in pregnancy. Additionally, comprehensive demographic and environmental risk factor data would be helpful.

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