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ORIGINAL ARTICLE

Toxoplasma gondii protects from IgE sensitization and induces Th1/Th2 immune profile

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Abstract

Toxoplasma gondii (*T gondii*) infection has been associated with protection against allergy and autoimmune diseases. We investigated the effects of *T gondii* infection on cytokine and antibody responses in atopic and nonatopic Brazilian subjects. We have measured in whole-blood cultures, Th1 (IFN-γ and IL-12), Th2 (IL-5) and regulatory cytokine IL-10 in blood cells unstimulated and stimulated with pokeweed mitogen or *T gondii* soluble tachyzoites antigen (STAg) or *Dermatophagoides pteronyssinus* antigen. A significant negative association was found between high levels of anti-dust mite IgE and *T gondii* seropositivity (OR = 0.46; 95%CI = 0.25-0.85). STAg stimulation induced a mixed profile of Th1 and Th2 cytokines (IFN-γ, IL-12 and IL-5) in Tg-positive atopic individuals compared with Tg-negative atopic individuals ($P < .0001$, $P = .033$ and $P = .003$, respectively). In contrast, IL-10 production was not different between these groups. No association was found between *T gondii* infection and asthma. We hypothesized that the protective effect on atopy might be related to the strong Th1 immune response to *T gondii* found on the seropositive subjects. From our knowledge, this is the first study to investigate the association between atopy and *T gondii* infection in Brazilian subjects, analysing the cellular immune responses.

KEYWORDS
allergy, asthma, cytokine, immunoregulation, toxoplasmosis

1 | INTRODUCTION

The incidence of chronic inflammatory disorders, including allergic disorders (asthma and hay fever) and autoimmune diseases, has been increasing markedly at the global level.[1] The reasons for the increased prevalence of allergy are still not well understood.[2] A better understanding of the causes and risk factors related to this growing epidemic is fundamental for the development of a practical approach for the prevention of such conditions. Environmental changes that occurred in the last decades are likely responsible for these differences, such as urbanization, better housing, diet and fewer exposures to chronic infections.[3] There is a link between increased allergy and a reduction of some infections in Western countries.[2] However, the findings from epidemiologic studies for these epidemics remain inconclusive about specific agents and the mechanisms.[4]

According to the hygiene hypothesis, the increased prevalence of the atopic disease in developed countries is caused by a decrease in exposure to infections.[5] The initial mechanistic explanation of the hygiene hypothesis had an emphasis on the role of Th1 cells in regulating Th2 responses. Moreover, it now highlights the role of regulatory T cells in the regulation of both Th1- and Th2-induced inflammatory responses through mechanisms that include the production of regulatory cytokines.[6]

Exposure to pathogens transmitted by orofecal route or foodborne transmission, such as *Toxoplasma gondii*, has been shown to

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protect against the development of autoimmune and allergic diseases in experimental animal models.[2,7,8] Some evidence in support of this hypothesis has been observed in human populations.[4,5,9-11] However, the results obtained so far by different research groups are inconsistent.[12-14] The most common aeroallergen worldwide is *Dermatophagoides pteronyssinus*. It is considered a significant source of inhaled allergens, inducing airway allergen sensitization in genetically predisposed individuals.[11] In the present study, we hypothesize that T *gondii* infection may be regulating allergic sensitization. Therefore, we compared cytokine profiles from whole-blood cultures stimulated with *T gondii* soluble tachyzoites antigen (STAg) and *D pteronyssinus (Dp)* extract and the antibody responses against STAg.

2 | MATERIAL AND METHODS

2.1 | Study population

This study was performed in the city of Salvador in Northeast Brazil, which has a population of 2,953,986 inhabitants, according to 2017 estimates. In summary, the study population included 202 individuals that were assessed and divided into atopics or nonatopics (based on markers of allergy, skin prick test and IgE anti-*D pteronyssinus*) and seropositive or seronegative to *T gondii*, according to the infection marker used (serum IgG anti- *T gondii* detected by indirect ELISA). The study included individuals participating in the *Programa para o Controle da Asma na Bahia* (ProAR, Bahia State Asthma Control Program), as well as healthy individuals, making an ideal setting for the study of the issues raised in this work. Two faecal samples were collected from each individual and tested for eggs and larvae of soil-transmitted helminths, using the well-known spontaneous sedimentation technique. However, all samples were negative for helminth parasites. Standardized questionnaires were provided to collected data on demographic and social variables. Ethical approval was provided by the Ethical Committee of the Instituto de Saúde Coletiva, Universidade Federal da Bahia and by the Brazilian National Ethical Committee CEP/MCO/UFBA (Protocol 095/2012), and written informed consent was obtained from all participants.

2.2 | Collection of blood and skin prick test (SPT) exams

Blood was collected for antibody detection, to perform whole-blood culture (both described below in detail) and skin prick testing (SPT), as described by Lima-Matos and collaborators.[15]

2.3 | Measurement of specific IgE to *Dermatophagoides pteronyssinus*

Measurement of the levels of specific IgE (sIgE) to *D pteronyssinus* was performed using the ImmunoCAP assay (Phadia Diagnostics AB, Uppsala, Sweden). We used three cut-off points for aeroallergen-specific concentrations (>0.7 kU/L, >1.2 kU/L and >3.5 kU/L) to investigate their association with *T gondii* seropositivity, according to Mendonça et al.[16]

2.4 | Definition of asthma and atopy and asthma phenotypes

The samples of subjects with asthma were randomly selected from the population of a case-control study, as reported elsewhere. In brief, the cases with severe asthma were selected from the outpatient clinic of the Program for Control of Asthma in Bahia (ProAR) established from 2003, in the city of Salvador, Brazil. ProAR is a public secondary care outpatient reference centre specialized in asthma in Salvador and receives patients with uncontrolled asthma, usually demanding emergency visits and hospitalization. The criteria for patient admission in the clinic had to be in severe asthma condition, according to classifications available prior to 2003 by NIH and GINA. As these individuals are underprivileged users of the public health system and had no access to adequate treatment before admission, they met the criteria proposed by WHO for untreated severe asthma.[17] There were two control groups in the study. One comprising subjects with mild to moderate asthma, most of them controlled only with low-dose or without inhaled corticosteroids. The second control group comprised subjects without asthma. The enrolment period for the case-control study was from January 2013 to July 2015. The Institutional Review Board of the Federal University of Bahia and the National Review Board approved the study (CONEP 450/10), and all subjects signed informed consent. Atopy was defined by any positive response to a panel of 15 relevant aeroallergens, as previously described.[18] All individuals performed spirometry and had their response to a bronchodilator evaluated. The immediate response to a bronchodilator is one of the criteria for confirmation of the diagnosis of asthma according to the GINA.[19]

2.5 | *Toxoplasma gondii* soluble tachyzoite antigen (STAg) preparation

Animal care and experimental procedures were carried out in strict accordance with the recommendations of the Conselho Nacional de Controle de Experimentação Animal (CONCEA)—Brazil. The protocol conducted in this study was approved by the Ethics Committee in Animal Experimentation (CETEA) of the Universidade Federal de Minas Gerais, Brazil (Protocol CEUA 348/2012). Mice were supplied with water and food ad libitum and maintained under a 12 h light/12 h dark-light cycles. All efforts were made to minimize animal suffering during the course of this study. Euthanasia was performed by an intraperitoneal (i.p.) overdose of ketamine and xylazine duly approved by CETEA/UFMG. STAg was obtained from tachyzoites collected in the peritoneal exudate of two mice infected with *T gondii* (RH strain). To collect the exudate, 3 mL of

PBS pH 7.2 was injected into the animal's peritoneal cavity. The peritoneal liquid was recovered and centrifuged at 10 min for 600 *g*. Tachyzoites were separated from host cells by low-speed centrifugation (70 *g* for 5 min) and pelleted again at 10 min at 600 *g*. Finally, parasites were resuspended to 1×10^8 tachyzoites per 1 mL of PBS and then sonicated at 20 Hz (in an ice bath) for five cycles of 45 seconds, with two minutes intervals between cycles (Ultrasonic Homogenizer – 4710; Cole Palmer Instrument Co.). The protein concentration was measured by the Lowry method.[20]

2.6 | Blood collection and whole-blood cells cultures

The venous blood was collected into heparinized tubes and cultured at a dilution of 1:4 in RPMI (Gibco) containing 10 mM glutamine (Sigma-Aldrich) and 100 μg/mL gentamicin (Sigma-Aldrich) in the presence of soluble tachyzoites antigen of *T gondii* (STAg; 10 μg/mL), extract of *D pteronyssinus* (Dp; 10 μg/mL), pokeweed mitogen (PWM; Sigma-Aldrich; 2.5 μg/mL) or medium alone. The cells were cultured within 6 h of collection and were maintained in a humidified environment of 5% CO2 at 37°C for 24 h for detection of IL-10, IL-5, IL-12, IFN-γ.[21]

2.7 | Cytokine production

We measured the production of IFN-γ, IL-12, IL-5 and IL-10, in whole-blood cell culture supernatants, using commercially available antibody pairs and recombinant cytokine (BD Pharmingen for IFN-γ, IL-12, IL-5) and (eBioscience Inc, for IL-10), by sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions. Cytokine concentrations were determined by interpolation of standard curves. The detection limits (low/high) in pg/mL for each cytokine were as follows: IFN-γ (4.7/300), IL-12 and IL-5 (7.8/500) and IL-10 (4.7/300). The concentration values of the cytokine production by the antigen-stimulated cells were obtained after subtraction by the concentration values of the respective cytokine production by nonstimulated cells (background).[21] To evaluate the cellular immune responses, the 108 subjects were divided into four groups, atopic *T gondii*-positive, atopic *T gondii*-negative, nonatopic *T gondii*-positive and nonatopic *T gondii*-negative.

2.8 | ELISA to detect serum anti-*T gondii* IgG and avidity IgG

The ELISA and the avidity IgG tests were carried out as described by Buery and collaborators [20] with some modifications. Flat-bottomed 96-well polyethylene microplates (Sarstedt®) were previously sensitized with STAg (0.5 μg of protein/well) overnight at 4°C. All serum samples were tested in duplicate in a dilution of 1:100 using a peroxidase-labelled anti-human IgG conjugate. Readings were done at 490 nm in an ELISA plate reader (Bio-Rad®, Model 3550). The cut-off value for the assay was calculated as the mean absorbance of serum samples obtained from eight serum samples negative for *T gondii* IgG, plus three standard deviations. The results were expressed as reactivity indexes (RI) according to the formula: RI = OD sample/ OD cut-off, where RI values > 1.0 were considered positive. Avidity IgG (expressed in %) was measured by average absorbance for each urea-treated serum (AU) in relation to the average absorbance of each urea not treated serum (A): AU/A X 100. Avidity values > 50% indicate chronic toxoplasmosis, whereas values < 50% suggested recent toxoplasmosis. To minimize the time required and to use the same control for both assays, both tests described above (ELISA to detect IgG and the IgG avidity test) were performed on the same plate.

2.9 | Statistical analysis

For the association of *T gondii* seropositivity with asthma, asthma morbidity and atopic markers, univariate and multivariate analyses were made using logistic regression. The confounder variables were sex, age, schooling and income. Statistical analyses used a significance level of 5% and were performed using the Statistical Package for Social Sciences – SPSS, v. 17.0 and Graph Pad 5.0. Statistical analyses used a significance level of 5% and were performed using the Statistical Package for Social Sciences—SPSS, v. 17.0.

To evaluate differences in cytokine production in stimulated and nonstimulated culture, the Kolmogorov-Smirnov test was applied for test normality, and then the nonparametric strategy was applied by using Mann-Whitney test in Graph Pad 5.0 program.

3 | RESULTS

3.1 | Demographic data of the study population and *Toxoplasma gondii* seropositivity

The demographic and social variables, as well as the seropositivity status of the study population, are presented in Table 1; 85.64% of the subjects were female, 50.0% aged less than 45 years, education above complete first grade was found in 82.67%, and 37.1% of families earned less than 270 US dollar monthly; 62.9% of the subjects were positive for serum IgG anti-*Toxoplasma gondii* and 100% of the positive IgG individuals had high avidity, which means they had chronic *T gondii* infection (data not shown). The prevalence of IgG seropositivity against *T gondii* increased with ageing ($P = .001$).

3.2 | Levels of anti-*Toxoplasma gondii* IgG in atopic and nonatopic subjects

Figure 1 shows that levels of IgG to *T gondii* were significantly higher in nonatopics than in atopics individuals ($P = .022$).

Table 2 shows the association for both crude and adjusted analyses of *T gondii* infection with specific IgE adjusted for gender, age, total income

TABLE 1 Study population characteristics according to *Toxoplasma gondii* seropositivity

Population characteristics	Seropositivity to *Toxoplasma gondii*		
	T gondii-positive	*T gondii*-negative	*P* value[a]
Age			
≥45 years old	75 (74.3)	26 (25.7)	.001
<45 years old	52 (51.5)	49 (48.5)	
Gender			
Female	111 (64.2)	62 (35.8)	.408
Male	16 (55.2)	13 (44.8)	
Schooling			
≤1 st complete[b]	26 (74.3)	9 (25.7)	.177
>1 st complete	101 (60.5)	66 (39.5)	
Income			
≤270 USD monthly	52 (69.3)	23 (30.7)	.175
>270 USD monthly	75 (59.1)	52 (40.9)	
Total	127 (62.9)	75 (37.1)	

[a]Chi-square test/Fisher's test.
[b]First grade education.

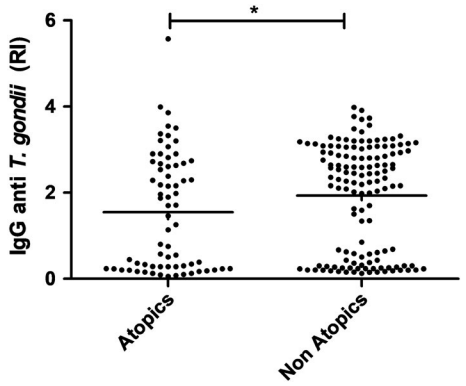


FIGURE 1 Distribution of reactivity indices (RI) response of anti-*Toxoplasma gondii* IgG among atopic (n = 69) and nonatopic (n = 133) subjects. An association between IgG levels and atopy using Mann-Whitey nonparametric test show a statistically significant difference in IgG levels between the two groups (*P* = .022), atopics presenting a lower IgG response (mean RI = 1.548) than non-atopics (mean RI = 1.934)

and schooling. Using a cut-off point of ≥ 0.70 kU/L, ≥ 1.20 kU/L, ≥ 3.50 kU/L, it was observed that 55.5%, 53.6% and 49.7%, respectively, had specific IgE for *D pteronyssinus*. Positive SPT for *D pteronyssinus* was present in 54.4% of the subjects. No association between *T gondii* infection and atopy was found using ≥ 0.70 kU/L sIgE, for both crude and adjusted analyses. At ≥ 1.20 kU/L sIgE cut-off and SPT, only the crude analysis was statistically significant. Meanwhile, associations at ≥ 3.50 kU/L sIgE cut-off were found in both crude and adjusted analyses (crude OR = 0.42; 95%CI = 0.23-0.76; Adjusted OR = 0.46; 95%CI = 0.25-0.85), indicating a negative association of high levels of anti-dust mite IgE and *T gondii* infection.

On the other hand, only the crude model showed a negative association between SPT positivity and seropositivity for toxoplasmosis (crude OR = 0.55, 95%CI = 0.31-0.99).

TABLE 2 Association between biomarkers of atopy and seropositivity to anti-*Toxoplasma gondii* IgG antibody

		Seropositivity to *T gondii*		
	N	N (%)	Crude OR (CI)	Adjusted OR (CI)[b]
sIgE ≥ 0.70[a]				
Yes	90	50 (55.5)	0.57 (0.32-1.01)	0.65 (0.35-1.18)
No	112	77 (68.7)	1	1
sIgE ≥ 1.2				
Yes	82	44 (53.6)	**0.52 (0.29-0.94)**	0.58 (0.32-1.06)
No	120	83 (69.1)	**1**	1
sIgE ≥ 3.5				
Yes	69	34 (49.7)	**0.42 (0.23-0.76)**	**0.46 (0.25-0.85)**
No	133	93 (69.9)	**1**	**1**
SPT[c]				
Yes	79	43 (54.4)	**0.55 (0.31-0.99)**	0.65 (0.35-1.19)
No	123	84 (68.3)	1	1

Note: Statistically significant association in bold (*P* < .05).
[a]*D pteronyssinus*.
[b]Adjusted for gender, age, total income and schooling.
[c]Skin prink test *D pteronyssinus*.

3.3 | Association between *Toxoplasma gondii* infection and asthma

Among individuals with *T gondii* infection, 64.85% were considered asthmatics. In which 22.77% had mild to moderate asthma, 35.15% severe asthma with airway obstruction reversibility and 6.93% severe asthma without reversibility. The remaining 35.15% were

nonasthmatic. No association was found between *T gondii* infection with asthma and their phenotypes (Table 3).

3.4 | Cytokine profile

To measure the impact of *T gondii* infection on cytokine production in whole-blood cultures, we measured Th1 (IFN-γ, IL-12), Th2 (IL-5) and Treg (IL-10) cytokines.

After stimulation with STAg, elevated IFN-γ, IL-12 and IL-5 levels were detected in atopic *T gondii*-positive patients compared with atopic *T gondii*-negative patients ($P < .0001$, $P = .033$ and $P = .003$), respectively (Figure 2A,B,D). In contrast, levels of cytokine IL-10 was equal between these groups ($P > .05$) (Figure 2C). No statistical difference was detected in cytokine levels following *D pteronyssinus* stimulation in *T gondii*-positive atopic versus *T gondii*-negative atopic individuals (Figure 2A-D).

When comparing the nonatopic *T gondii*-positive group versus the nonatopic *T gondii*-negative group, we observed a statistically significant difference only for IFN-γ levels after STAg stimulation ($P < .0001$) (data not shown).

No difference in cytokine secretion differ between the different groups of individuals in both unstimulated and PWM-stimulated whole-blood cultures.

4 | DISCUSSION

In this work, we have found a 62.9% seroprevalence for anti- *T gondii* IgG, all in the chronic phase of *T gondii* infection, since the anti-*T gondii* IgG found in this population was of high avidity. The individuals with older age were more likely infected, regardless of gender. These findings corroborate previous reports, which claim that this infection affects 50%-70% of the Latin-American adult population and reflects a higher chance of exposure to the parasite with increasing age.[20,22-25] The primary source of infection in Brazil is probably caused by the ingestion of oocyst-contaminated water.[26]

Our results have shown a negative association between *T gondii* infection and atopy (sIgE alone) by analysing the humoral immune responses. Furthermore, higher levels of parasite-specific IgG among nonatopic subjects was observed. Alcantara-Neves et al and Fernandes et al and [4,11] reported that the presence of a serological marker of chronic infection in toxoplasmosis was inversely related to the allergenic sensitization. These findings support that the Th1-type of the immune response induced by a pathogen such as *T gondii* may exert inhibitory effects on the induction of mite allergen sensitization or reactivity. Our findings are in agreement with some studies that have provided evidence for strong inverse associations between *T gondii* infection and atopy markers.[4,5,9-11] However, some other studies have also found negative or inconclusive results regarding this matter.[12-14]

We also found that neither asthma nor asthma phenotypes were associated with *T gondii* infection. These findings corroborate the results in Alcantara-Neves et al,[4] which found that this infection was not associated with current wheezing. Although, these findings of no significant association with asthma are contrary to those reported by Matricardi and collaborators.[9] Maybe due to population differences, the number of individuals of the study groups (Alcantara-Neves et al 2012), or the difference in causes of asthma in Latin America that lead to various phenotypes of this disease, for example nonatopic asthma. Fenoy et al,[2] using a well-known murine model of allergic lung inflammation, have shown that both acute and chronic infection with *T gondii* substantially blocked the development of airway inflammation and was related to high levels of INF-γ induced by the parasite. As shown in Fernandes et al 2010,[11] we also observed high production of IFN-γ after STAg stimulation in *T gondii*-positive individuals, regardless of whether they are atopic or not. These data are in agreement with the literature, that is IFN-γ mediates the protection against *T gondii*, and it is capable of suppressing the Th2 profile. These data contribute to the hypothesis that *T gondii* protects against atopy.[27]

Stimulation with STAg showed a predominant synthesis of the cytokine IL-12 in atopic *T gondii*-positive patients compared with atopic IgG anti- *T gondii*-negative patients. Sher et al [28] highlighted the importance of IL-12 in resistance to infection by *T gondii*. As far

TABLE 3 Association between asthma phenotype and seropositivity to *Toxoplasma gondii* IgG antibody

Asthma phenotypes	N	Seropositivity to *T gondii* N (%)	OR (CI)	$OR_{adjusted}$ (CI)[a]
No asthma	71	43 (61.4)	1	1
Mild to moderate asthma	46	24 (54.0)	0.71 (0.34-1.50)	0.75 (0.35-1.61)
Severe asthma with reversibility[b]	71	50 (70.4)	1.55 (0.77-3.11)	1.00 (0.45-2.24)
Severe asthma with no reversibility	14	10 (69.2)	1.63 (0.46-5.70)	0.99 (0.26-3.76)
Atopic asthma[c]	59	31 (52.5)	2.58 (0.61-10.97)	1.68 (0.35-8.15)
Non-atopic asthma	72	53 (73.6)	1.46 (0.70-3.08)	1.13 (0.50-2.56)

[a]Adjusted for gender, age, total income and schooling.

[b]Diagnosis validated by spirometric criteria based upon bronchodilatation after inhalation of a bronchodilator.

[c]SIgE *D pteronyssinus* cut-off 3.5 KU/L.

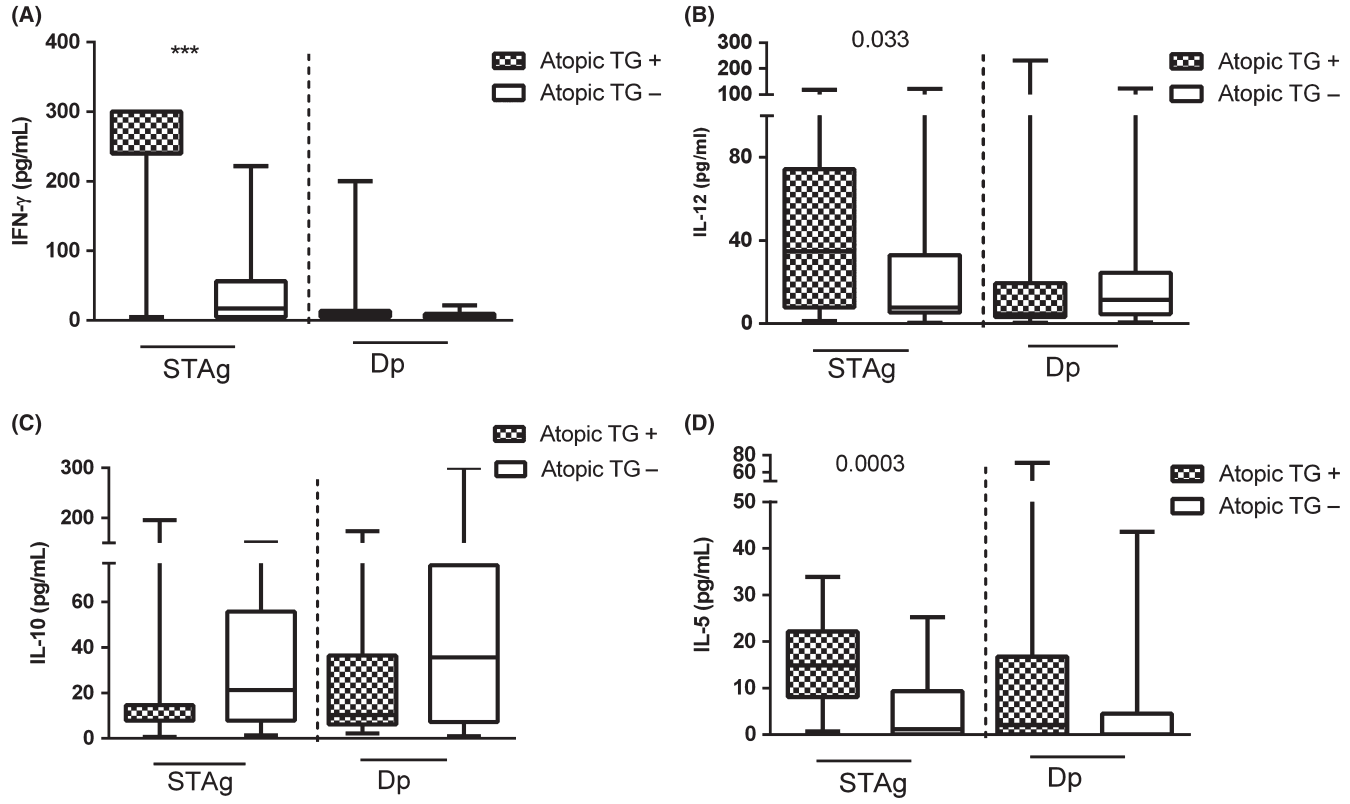


FIGURE 2 Cytokine levels in whole-blood cultures supernatants of 108 individuals distributed in two groups according to allergy and infection markers: atopic *Toxoplasma gondii*-positive (TG +) and atopic *T gondii*-negative (TG –). Cells were stimulated with pokeweed mitogen (PKM; 2.5 μg/mL), *T gondii* soluble tachyzoite antigen (STAg; 10 μg/mL) or *Dermatophagoides pteronyssinus* allergen extracts (DP; 10 μg/mL). Supernatants were collected after one day of culture and analysed for detection of IFN-γ (A), IL-12 (B), IL-10 (C) and IL-5 (D). ***0.0001

as we have observed in the literature, this was the first study to investigate the association between atopy, asthma, *T gondii* infection and IL-12 production.

Similarly, atopic *T gondii*-positive patients also produced IL-5 levels high in response to STAg. Matowicka-Karna reports that patients infected with *T gondii* had twofold higher values of IL-5 as compared to healthy subjects and IL-5 is the major cytokine responsible for the increase in the eosinophil population in parasitosis.[29]

The proposed mechanism for the hygiene hypothesis, as previously commented, is related to regulatory cytokines such as IL-10 and TGF-B, which might inhibit allergic diseases, has received growing support information from animal studies.[2,8] However, we did not find significant difference between the studied groups concerning regulatory cytokines, which corroborates Fernandes et al (2010) data, who have reported that despite no significant differences found among the evaluated groups, the role of regulatory cytokines such as IL-10, cannot be ruled out and deserves further investigations.[11]

To our knowledge, this is the first study to investigate the association between atopy, asthma and *T gondii* infection in Brazilian subjects, analysing the cellular immune responses. Our results support epidemiological studies that claim *T gondii* infection protects people from allergy.[4,5,10,11] Further studies should be conducted to evaluate the molecular mechanisms involved in this process, contributing to the development of interventions with great potential in primary and secondary prevention of allergic diseases.

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CONFLICT OF INTEREST

The authors have stated that there is no conflict of interest in connection with this article.

DISCLOSURES

None.

AUTHOR CONTRIBUTION

All authors have actively participated in the analysis of research results and approve this manuscript version. Milena de Medeiros Clemetino Andrade, Álvaro Augusto Cruz and Camila Alexandrina Figueiredo were responsible for study design. Milena de Medeiros Clemetino Andrade, Alana Alcantara Galvão and Thales Reis Fonseca have conducted the fieldwork, managed the database and performed the experiments. Ricardo Wagner de Almeida Vitor and Neuza Maria Alcantara-Neves e Camila Alexandrina

Figueiredo were responsible for the supervision of the fieldwork and laboratory experiments. Milena de Medeiros Clemetino Andrade, Valdirene Leão Carneiro and Álvaro Augusto Cruz e Camila Alexandrina Figueiredo were responsible for data analysis and writing the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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