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EVALUATING THE CORRELATION BETWEEN IGG ANA IGE RESPONSES IN A RURAL IRAQI POPULATION INFECTED WITH ENTEROBIUS VERMICULARIS

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Abstract. Background: Helminths induce an immune response that is typically characterized as a Th2 response with elevated levels of specific antibodies. The interrelationship of total IgE and enterobiasis-specific IgG has been studied poorly to date. A global survey of research indicates that E. vermicularis infection continues to be among the most common helminthic parasites infecting humans globally, but it is especially prevalent in children. Objectives: The purpose of this research was to assess total serum IgE and specific (anti- Enterobius) IgG in infected subjects and to analyze whether there is an association between those antibody responses and Th2-mediated humoral immune response. Methods: This study used a cross-sectional approach in Mosul, Iraq, which involved 32 confirmed E. vermicularis infected subjects, and 36 control subjects who had no E. vermicularis infection. Total serum IgE and specific anti-E. vermicularis IgG concentrations were assessed by quantitative ELISA. Statistical analyses were conducted with t-tests for two means, ANOVA to compare three or more means, Pearson's correlation, and linear regression. Results: In comparison to healthy control subjects, individuals who had been infected showed significantly greater amounts of total IgE (422.0±41.3ng/ml), as well as a significantly greater amount of

specific IgG (2,840±320ng/ml) (p<.001). The level of IgE was found to be at least nine times that of the level found in healthy control subjects; likewise, IgG levels were shown to be at least three times those of healthy controls. In addition to demonstrating this difference, a statistically significant positive relationship was also demonstrated for the levels of IgE and IgG among the infected subjects (r=0.68,p<.001); specifically, IgG explained 46% of the variation in IgE levels (R^2=.46). Conclusions: Total IgE and specific anti- Enterobius IgG levels increase simultaneously with E. vermicularis infections, which indicates an activation of the Th2 mediated humoral immune response; therefore, this study contributes to our knowledge regarding host-parasite immunodynamics and may help us understand better how antibodies are regulated during enterobiasis.

Key words: Enterobius vermicularis; enterobiasis; total IgE; specific IgG; ELISA; Th2 immune response; humoral immunity; helminth infection.

Introduction

Enterobius vermicularis (pinworm) is an extremely common gastrointestinal helminthic infection around the world. It occurs predominantly in children across both temperate and tropical zones [1,2], although iit can affect people of all ages. Pinworms are generally viewed as a benign parasitic condition, but because they have such a high degree of contagiousness; recur frequently due to poor hygiene practices; and create a significant risk for poor health conditions, it is still a considerable public health problem [3, 4].

Helminths elicit a wide array of immunologically-mediated interactions with their hosts. Typically, when exposed to helminthic antigens, an individual's immune response will be driven towards a Th2-dominant response [5,6]. The Th2-polarized response is primarily regulated through the action of several cytokines including IL-4, IL-5 and IL-13 that induce B cell proliferation and the class-switching of antibodies. Immunoglobulins of the IgE subclass are one of the hallmarks of a Th2-driven immune response; these immunoglobulins play a major role in anti-helminthic defense through mast cell activation, recruitment of eosinophils for parasitic destruction and ultimately parasite expulsion [7,8].

In addition to IgE, Immunoglobulin G (IgG) antibodies also play a role in host defense mechanisms through their roles as complement activators, antigen neutralizers and mediators of Antibody-Dependent Cellular Cytotoxicity (ADCC) . Following prolonged antigen exposure during Helminthic infections, IgG responses against the infecting parasites may be generated, indicating that there is an ongoing adaptive humoral immune response. The relationship between elevated levels of total IgE and parasite-specific IgG responses in Enterobiasis has however been inadequately characterized [9,10].

The majority of past studies has mainly emphasized increased levels of IgE due to Enterobiasis, while a number of studies have been conducted to assess IgE and *enterobius vermicularis* specific IgG responses as a group for quantification of relationships between them [11,12]. Investigating if such humoral immune responses are independent of one another or cooperative could be important for understanding the immunoregulatory mechanisms that underlie Th2 mediated humoral response

Therefore, this study evaluated both the levels of total serum IgE as well as the levels of the anti-Enterobius (specific) IgG antibodies found in the serum of people who were infected by *Enterobius vermicularis* and examined whether there is a

relationship between the two types of antibody response. The study also looked at how age and gender might influence antibody production.

Materials and Methods

Study Design and Participants

Participants were recruited in a cross-sectional design, in Mosul, Nineveh Governorate, Iraq in 2024. Of the 68 participants; 32 had confirmed infections of *Enterobius vermicularis*, while 36 were apparently healthy controls.

Of those that had confirmed *Enterobius vermicularis* infections, there were 14 male and 18 female participants ranging from ages 3 to 45 years old. The confirmation of *Enterobius vermicularis* infections was completed through the use of the cellophane tape (Graham) method where the E. vermicularis eggs were identified microscopically. The control group was demographically representative (for age and gender), but the results of their stool examinations indicated no evidence of an intestinal parasite or symptomatic evidence of enterobiasis.

Inclusion and Exclusion Criteria

Women who are pregnant and those with a history of immunodeficiency disorders; chronic inflammation or autoimmune disease; have been vaccinated in the last month; or have current bacterial/viral infection were excluded from participating. All participants were also excluded if they had received an antiparasitic medication in the past three months.

Ethical Issues

All of the adult participants had written informed consent. For minors, a parent or legal guardian gave informed consent. The study followed ethical guidelines that are standard for biomedical research.

Sample Collection and Serum Preparation

Five mL of venous blood was taken aseptically in duplicate (i.e. two different tubes) from each subject. Samples were allowed to clot at room temp; they then were spun down at 3000 RPM for ten min to allow separation of the serum. Serum samples were then frozen in aliquots and stored at -20°C until analyzed.

Quantification of Serum Total IgE

Total IgE levels in sera were determined by ELISA kit (BT LAB, China), which is an ELISA kit for quantitatively measuring total IgE levels in sera. The measurement of total IgE levels in sera involved the addition of standards and diluted serum samples (diluted 1:10) into wells that had been coated with capture antibody directed against human IgE and incubation at 37°C for 90 min. Wells were washed after incubation and then developed with HRP conjugate secondary antibody; this step also included incubation at 37°C for 60 min. TMB was employed as a substrate for color formation. Color reactions were terminated by adding sulfuric acid. Absorbances at 450 nm were recorded with a BioTek ELx800 microplate reader. Concentrations of total IgE in sera were calculated based on calibration curves and corrected for total dilutions. Values are presented as ng/mL.

Quantification of Serum Specific Anti–Enterobius IgG

Serum-specific Enterobius IgG antibody levels were quantitatively measured using an ELISA Kit manufactured by BT LAB of China. The ELISA Kits were used as per the manufacturer's guidelines. Concentration values were determined using the optical density (OD) reading at 450nm and subsequent reference to the standard curve created.

Concentrations were expressed in micrograms/ml; however, all concentration data were converted into nanograms/ml for purposes of statistical analysis. All data points collected are well within the range of the ELISA Kit's specifications and consistent with our laboratory protocol. Quality Control measures were also taken during each ELISA run.

Statistical Analysis

Statistical analysis was done in SPSS software v. 26.0 (Armonk, New York; IBM Corp.). Normality was assessed on continuous data with the use of the Shapiro-Wilk test. Normally distributed continuous data are reported as the Mean ± Standard Deviation. In cases where there is an issue with non-normal distribution, a Logarithmically transformed variable will be tested parametrically.

The comparison of each group (infected vs. Control) is done using Independent-Sample T-Tests. ANOVA (One Way Analysis of Variance) is utilized to compare age and gender subgroups. The correlation between Total IgE and Specific Enterobius Anti-IgG is determined by Pearson's Correlation Coefficient. A linear Regression Analysis is also performed to determine R2 (the percentage of the variation explained).

The sample size was determined by G*Power software version 3.1. Using an effect size of 0.8, $\alpha = .05$, and a power of 0.8; it was found that at least 26 subjects per condition would be needed to achieve the desired power for this study. All of the statistical tests utilized in this study used two-tailed tests. Statistical significance was defined as values less than or equal to 0.05. Where possible, values of $p < 0.001$ are reported to indicate strong evidence against the null hypothesis.

Results

Demographic Characteristics

In the study a total of 68 participants participated in this study; that is, 32 individuals who had *Enterobius vermicularis* infections and 36 healthy volunteers. The subjects with E. vermicularis were comprised of 14 male participants and 18 female participants, ranging in age from 3 to 45 years. In addition, the age and sex distributions among those without E. vermicularis (the controls), were equivalent to the distributions for those with the parasite.

Serum Total IgE Levels

Serum Total IgE levels are significantly greater in those infected with E. vermicularis than in controls. The mean IgE level for those that are infected was found to be 422.0 +/- 41.3 ng/ml; whereas controls were significantly less at a mean of 46.3 +/- 8.31 ng/ml ($p < .001$). This is indicative of an almost nine times greater IgE response by the body of those who have become infected.

Serum Specific Anti–Enterobius IgG Levels

Similarly, there was an increased concentration of serum–specific anti-Enterobius IgG levels found in the infected population as opposed to the uninfected. There were an average of 2,840 ± 320 ng/mL for the infected populations. The uninfected population had an average of 890 ± 145 ng/mL ($p < .001$) indicating that the antibody response to the parasites was elevated over three-fold.

Table 1. Comparison of Total IgE and Specific Anti–Enterobius IgG Levels Between Infected and Control Groups (Mean ± SD)

Parameter	Infected (n=32)	Control (n=36)	p-value
Total IgE (ng/mL)	422.0 ± 41.3	46.3 ± 8.31	<0.001
Specific IgG (ng/mL)	2,840 ± 320	890 ± 145	<0.001

Values are expressed as mean ± SD. An independent-samples t-test was applied.

Correlation Between Total IgE and Specific IgG

A significant positive association existed between serum total IgE and Enterobius-specific IgG antibody levels in infected persons (Pearson's $r= 0.68$; $p < 0.01$) The linear regression model showed that Enterobius-specific IgG antibody levels were responsible for 46% of the variability in IgE levels ($R2 = .46$); this is consistent with a humoral immune response.

Gender-Based Differences in Antibody Responses

Gender-Based Analysis showed that there was a Statistically Significant difference in Antibody Levels in Infected Individuals. Males had Higher Total IgE (Mean of 509.0 ± 50.7 ng/mL), Than Females (Mean of 354.7 ± 32.1 ng/mL) ($p= 0.049$). Similarly, Specific IgG Concentration Was Also Significantly Higher In Males (Mean of 3120 ± 380 ng/mL), Then In Females (Mean of 2620 ± 285 ng/mL) ($p = 0.032$).

Table 2. Gender-Based Comparison of Antibody Levels in Infected Individuals (Mean ± SD)

Parameter	Males (n=14)	Females (n=18)	p-value
Total IgE (ng/mL)	509.0 ± 50.7	354.7 ± 32.1	0.049
Specific IgG (ng/mL)	3,120 ± 380	2,620 ± 285	0.032

Values are expressed as mean ± SD. An independent-samples t-test was applied.

Age-Related Differences in Antibody Responses

Children (5–15 years) had a larger total IgE level than did adults (≥16 years); the p value for this was 0.039. In addition, children exhibited greater IgG concentration than did adults; the p value for this comparison was 0.028. Therefore, age-based comparisons of both total IgE and specific IgG concentrations revealed that significantly higher levels were observed among younger individuals.

Table 3. Age-Stratified Analysis of Total IgE and Specific Anti–Enterobius IgG Levels Among Infected Participants (Mean ± SD)

Analysis performed among infected participants only. An independent-samples t-test was applied.

Parameter	5–15 years (n=25)	≥16 years (n=7)	p-value
Total IgE (ng/mL)	436.5 ± 43.9	371.0 ± 37.0	0.039
Specific IgG (ng/mL)	2,950 ± 340	2,480 ± 290	0.028

Values are expressed as mean ± SD. An independent-samples t-test was applied.

Discussion

The current research looked into humoral responses that were linked to a humoral immune response (specifically IgE) caused by an infection of *Enterobius vermicularis*, which was evaluated through assessment of serum total IgE as well as specific anti-Enterobius IgG in comparison to those who are uninfected. Both antibody types had significantly increased levels in infected subjects indicating that there is a higher degree of humoral immune activity driven by Th2. [13,14].

The high levels of total IgE found in the infected group is reflective of the long-established involvement of IgE in host-parasite relationships for many helminths. As is typical of parasitism (which is generally associated with an allergic response), parasitic infection promotes T helper type 2 (Th2) responses, which includes the release of IL-4, IL-5, and IL-13 cytokines. These cytokines result in class switching of activated B cells to produce IgE antibodies. This finding provides further support for the hypothesis that *Enterobius vermicularis* infection results in a strong immune activation that has features similar to an allergic reaction [15, 16].

In addition to elevated IgE levels, the researchers showed a significant increase in specific (anti- Enterobius) IgG. The difference between the overall level of IgG and "specific" IgG is that total IgG is an indicator of the overall amount of immunoglobulins being produced by an individual whereas parasite-specific IgG demonstrates that the adaptive immune system has identified helminth antigens. The fact that there was greater than a threefold increase in specific IgG shows that these individuals are continuously exposed to antigen from the parasite and the humoral immunity continues to be stimulated.

Importantly, it was observed to be positively correlated with a statistically significant relationship in-between the amounts of IgE and IgG (r= 0.68) as an overall measure, which indicates 46% of IgE variability is explained by the amount of IgG (R^2 = 0.46). This observation suggests a coordinated antibody response, instead of independent activation of immunoglobulin. Such parallel increase could indicate synchronized activation of B cells by Th2 mediated cytokine signaling. The level of correlation also supports the concept that enterobiasis will induce integrated humoral immunity modulating responses.

A gender-specific analysis demonstrated significantly higher antibody titers of male mice compared with female mice. The immunological variations observed in a number of species infected by helminths (a type of parasitic worm) often show sexual dimorphism; however, behavioral (exposure), as well as hormonal influences may also be contributing factors to the difference seen here. In addition to demonstrating sexual dimorphism, an age stratification of the data was performed and this revealed that young mice had significantly elevated antibody titers compared with adult. It is possible that there are increased risks for exposure, as well as a larger parasite load, in young [17].

Collectively, these results support the idea of a co-ordinated humoral response to E. vermicularis infection as demonstrated through increases in both total serum IgE and specific IgG against the parasite. In addition, this study provides evidence for the dynamic interaction between immediate hypersensitivity (anaphylactic) type reactions with long-term adaptive responses during enterobiasis [17,18].

Despite these caveats, there are some other limits to acknowledge. The limited sample size is likely to have an impact on the generality of our results. Furthermore, we did not assess cytokine profiles or quantify parasite burdens; this could provide additional mechanistic insights into how immune responses develop [19,20].

Conclusion

The increase of both total IgE and anti–Enterobius-specific IgG levels seen as an effect of *E. vermicularis* indicates that there was enhanced humoral immunity due to Th2. A positive relationship between the two types of antibodies suggest that the immune response was well-coordinated rather than being caused by the individual type of immunoglobulins produced.

There were also gender and age-related variations in the level of antibody that was created in response to infection, which could indicate that certain characteristics or conditions of the host influence the number of antibodies generated during an enterobiasis infection.

These results will help us understand the immune effects of pinworms and can provide evidence for using an antibody profile (together) to assess parasitic disease.

Future studies including larger populations and additional immunological markers are needed to identify the mechanisms regulating antibody creation/production in parasites.

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Conflicts of interest

The authors declare no conflict of interest.

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