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IgG Antibody Titers against *Ascaris lumbricoides*, *Strongyloides stercolaris*, and *Toxocara canis* in Venezuelan Patients with Asthma or COPD

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Abstract: It has been suggested that parasitic infections, common in Latin American populations, may amplify the inflammatory response of the airways. There are several reports in atopic and asthmatic patients, but few reports of parasitic infection in COPD patients. The study aimed to determine the prevalence of parasitic infections in COPD patients as compared to atopic and asthmatic patients attending the outpatient clinics of the Institute of Immunology and the pneumonology service of the University hospital. A case-control study was conducted: 100 patients with bronchial asthma, 100 patients with COPD, 100 individuals with atopy without respiratory symptoms, and 100 healthy individuals. Serum specific IgG antibody against the parasites Ascaris lumbricoides (Al), Strongyloides stercolaris (Ss) and Toxocara canis (Tc) were measured: by ELISA. IgE levels were used as an indirect indicator of atopy. Positive IgG for Al was observed in all groups, predominantly in atopic cohort, Ss positiveness was recorded only in 4 COPD patients and Tc positiveness was observed in all groups except in controls. There are significant correlations between the values of Al and IgE in controls, atopic and asthmatic patients not with COPD. No correlation was found for Tc. IgE levels and FEV1 correlate only in atopic and asthmatic patients. Parasitic infections are common in atopic patients and in moderate and severe asthmatic and COPD patients. Anti-inflammatory treatment may be responsible for the increase frequency of infection.

Keywords: COPD; asthma; atopy; eosinophils; IgE; *Ascaris lumbricoides*; *Giardia lamblia*; *Strongyloides stercolaris*; *Toxocara canis*

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a long-term inflammatory lung condition in which airflow is partially reversible [1–4]. Its symptoms include difficult breathing, coughing, mucus production, and wheezing [1–4]. COPD is mainly caused by prolonged exposure to irritating gases or particulate matter, usually from cigarette smoke [1–4]. COPD patients are at higher risk of developing heart disease, lung cancer, and other conditions [1–4]. COPD can also be related to asthma; COPD asthma overlap syndrome. Patients with COPD asthma overlap syndrome may differ from the classical COPD patients in clinical manifestations and response to treatment.

Emphysema and chronic bronchitis are the two most common conditions contributing to COPD [1,3–5]. These two conditions usually occur together and can vary in severity among individuals with COPD [1,3–5]. Chronic bronchitis is the inflammation of the lining of the bronchial tubes, which carry air to and from the air sacs (alveoli) of the lungs. It is characterized by a daily cough and mucus (sputum) production. Emphysema is a condition in which the alveoli at the end of the lungs' smallest

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air passages (bronchioles) are destroyed due to damaging exposure to cigarette smoke and other irritating gases and particulate matter. Although COPD is a progressive disease that worsens over time, it is treatable. With proper management, most people with COPD can achieve reasonable symptom control and quality of life, as well as reduce the risk of other associated conditions.

In recent years, it has become evident that a subgroup of COPD patients are atopic patients. In these patients, there is a need to control allergic reactions, which may increase respiratory inflammation. Type 2 inflammation assessment is also a part of the standard clinical control of COPD patients [6]. In general, the level of eosinophils in the blood is higher in COPD patients than in healthy subjects, although there is marked variability. Higher blood eosinophil values in patients with COPD are associated with a higher number of eosinophils in the airways [3,6]. Eosinophil count may explain the response to glucocorticoid treatment [3,7]. Moreover, peripheral blood eosinophil levels seem to define a type of COPD patient that appears to respond better in exacerbations, although it is more prone to be hospitalized [8]. In current guidelines for treating COPD, the blood eosinophil count is part of the initial assessment after diagnosing and treating COPD [3].

Asthma is a chronic lung condition characterized by recurring symptoms, reversible airflow obstruction, and easily triggered bronchospasms [9–11]. It is also a chronic respiratory condition characterized by symptoms like dyspnea, cough, and wheezing [9–11]. As spirometry shows, diagnosis requires consistent symptoms and variable expiratory airflow obstruction [9–11]. Treatment aims to control symptoms and prevent exacerbations based on symptom frequency and severity [9].

The development of asthma, often starting in childhood, involves a complex interaction of genetic and environmental factors related to atopy [9–11]. Researchers are working on predictive systems to identify individuals at risk of symptoms into adulthood [12–14]. Despite advancements in genetic and environmental factors, clinical strategies are lacking to reduce persistent asthma development [12–15]. This covers epidemiology, pathophysiology, assessment, pharmacological treatment, and monitoring strategies for adolescents and adults, aligning with recommendations from asthma organizations [9].

Intestinal nematode infections, particularly the most common one caused by the roundworm *Ascaris lumbricoides*, affect up to one-third of the global population. [16,17]. While most cases are asymptomatic, they can lead to pulmonary or severe gastrointestinal issues [16–18]. The infection is prevalent in areas with poor sanitation and is associated with malnutrition, iron deficiency anemia, and stunted growth and cognitive development [16–18]. As a consequence of infection, an increased number of peripheral eosinophils can be observed [19,20]. Aside from eosinophil count, antibodies against *Ascaris lumbricoides* may be related to allergic asthma [21].

Strongyloidiasis is an intestinal infection caused by the parasitic nematode *Strongyloides*. The most common pathogenic human species is *S stercoralis*, which can persist and replicate within a host for decades without causing symptoms in healthy individuals [22]; hyperinfection syndrome has been described [23]. Larvae access the host through the skin and travel directly to the lungs via blood vessels, generating inflammation and exacerbating current disease [24,25]. After spilling into the alveolar space, the larvae advance through the trachea and pharynx, where they are swallowed [24,25]. However, it can cause life-threatening infections in immunocompromised individuals [22,26]. The symptoms of strongyloidiasis include watery diarrhea, abdominal cramping, and urticarial rash [22]. Additionally, during chronic uncomplicated infections, the larvae may migrate to the skin, causing cutaneous strongyloidiasis, known as larva currens, due to the quick migratory rate of the larva [22]. The parasite can reinfect individuals if not properly treated [22].

Toxocariasis is a widespread zoonotic disease that humans can contract from dogs, cats, and wild hosts [27,28]. It is prevalent in less industrialized nations and affects children and immunocompromised individuals, commonly in underdeveloped countries; however, due to the increase in pets in households, infections in developed countries also occur [28,29]. Even though neurological and optical manifestations are common in Toxocara, infections have been related to allergic manifestations [30], and several reports have shown lung infection [31,32].

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Diagnosing most parasitic infections relies on stool analysis of the parasite or eggs. Parasite detection may require the analysis of serial samples to define infection. In recent years, the detection of parasite antigens in the stool has facilitated diagnosis, and the detection of antibodies against specific antigens has simplified the analysis and follow-up of patients. Considering the complexity of analysis in a large population of individuals attending the outpatient clinic of the Institute of Immunology and the pneumology service at the Central University Hospital in Caracas, we decided to analyze the levels of IgG antibodies against the three most relevant parasites that can be critical to screen in patients with asthma, COPD and atopic individuals. The FEV1 values of each individual, along with hematological values and IgE, were used to analyze the cohort and find possible correlations.

2. Materials and Methods

2.1. Human samples

The study is a case-control study involving four groups: 100 patients who met the criteria for asthma according to the guidelines [9,10]. In addition, 100 patients with COPD were classified according to the GOLD guidelines [1–3]. Patients were stable at the time of sample collection. As controls, there were 100 atopic patients, characterized as defined previously [33], without lung involvement and individuals with skin and food allergies; only 20 had mild chronic rhinitis without obstructive components. The patients showed no abnormalities in paraclinical analysis, indicating the absence of infectious or disease exacerbation. Pregnant patients, patients with cancer or other comorbidities, cardiovascular diseases, diabetes, and autoimmune disorders were excluded. These patients had been attending the outpatient clinic for at least a year.

Two 5 ml samples, in heparin for hematologic analysis and dry tube for serum were taken. The blood samples were taken when patients attended control medical checkups. Hematological counts were performed using the Beckman Coulter Ac.T Diff hematology analyzer. The serum of each sample was obtained after 30 minutes of sample collection by centrifuging clotted venous blood. The serum was stored at -70 degrees until the ELISA analysis was performed. The three ELISA kits were used to avoid sample freezing and thawing, which may alter the titters of IgG.

Written consent was obtained from all individuals interested in participating in the study. The study received approval from the Ethical Committee of the Institute of Immunology, Faculty of Medicine, Caracas, Venezuela (approval number 20052308).

2.2. ELISA kits and result analysis

Diagnosis of parasitic infection mainly relied on commercial immunological techniques. For *Ascaris*, the common ABA-1 antigen is used for screening; for Strongyloides, the antigen from *S papillosus* larvae antigen is used and for *T. canis* larval excretory-secretory antigen-based ELISA (TcES-ELISA). The following commercial kits were used: 1) MyBioSource for *Ascaris lumbricoides* (Al), 2) Abcan for *Toxocara canis* (Tc), and 3) Euroimmun for *S. stercolaris (Ss)*.

The tests were performed according to the manufacturer's guidelines. For the Mybiosource kit, the sera were diluted (1:100 v/v) with the buffer supplied by the provided, and it was added to the already treated ELISA plates. Five assay controls were used: a negative control, a certified pooled sample from certified negative individuals, a negative control of the kit, a positive control of the kit, and a certified sample from the Institute of Tropical Medicine, Faculty of Medicine. Universidad Central de Venezuela. In addition, the stool samples of the positive samples were analyzed by expert technicians of the Institute of Tropical Medicine using the standard techniques.

For the Abcan kit to assess *T. canis*, the sample dilution was carried out at 1:100 as suggested by the manufacturer, and the certified positive and negative controls were used along with the controls from the kit. The positive individuals were certified by the analysis performed by the Institute of Tropical Medicine, Faculty of Medicine. Universidad Central de Venezuela using the standard protocol [34] followed by ELISA [35].

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In both kits, the provider suggested that the data be calculated based on the optical density and that units define the value according to the formula. Using the controls established in our laboratory with our controls, the positive samples were > 12 Units.

$$\frac{\text{Patient (mean) absorbance value x 10}}{\text{Absorbance of the Cut-off}} = [\text{Units} = \text{U}]$$

The analysis of IgG against *S. stercoralis* was performed using the Euroimmune ELISA kit following the automated version. The results were only defined by positive or negative results confirmed by the proper controls from the kit and positive and negative samples from the Institute of Tropical Medicine. Faculty of Medicine. Caracas.

Total IgE was assessed using the ELISA kit from Thermo-Fisher, following the suggested protocol with minor modifications. The samples were calculated according to the instructions but then converted into IU/ml upon the request of the Ethical Committee since the values were given to the patients and had to be in the same range as the other tests performed with other kits. The conversion was done by using the calculation from the web page https://unitslab.com/.

2.3. Statistics

The results were analyzed using the Graph Prism Software version 5.0. One-way ANOVA was used to compare the different groups. The Chi-square test with Yate's correction was used to define the frequency of infection. In addition, the Pearson coefficient was used to calculate the quantitative values. The statistical difference is set to be $p<0.05$.

3. Results

The general characteristics of the population are illustrated in Table 1. The control group is composed of nonsmoker individuals. The gender was similar in the four groups. The age difference refers to the difficulty of proper controls without comorbidities above 60 years.

Table 2 depicts the hematological values recorded for the different groups. Several significant differences were recorded in the percentage of neutrophils and eosinophils. There were no differences in total lymphocytes or monocytes percentages.

Table 3 illustrates the frequency of parasite infection in the cohort. Atopic individuals with high IgE levels had the highest prevalence of *Al* infection, and four patients were positive for Tc. Significant differences were recorded in the frequency of *Al* infection as compared to controls ($p<0.0001$). No infection of Ss was recorded.

Table 4 shows the number of individuals with asthma or COPD infected with the different parasites. There was no significant difference when the frequency of infection was compared between asthma and COPD; however, both frequencies significantly differed from those of the atopic group ($p<0.0001$). The number of individuals that record positive antibodies to TC is similar between asthma, COPD, and atopy groups. Only 4 patients with positive antibodies against Ss in COPD significantly differs from the other 3 groups ($p<0.01$). Interestingly, only 4 individuals in the atopic and 4 in the asthma groups are positive for 2 parasites. Based on the confirmatory tests, it is very probable that both parasites infected these individuals.

Table 5 shows the different correlations with age, IgE, FEV1, and the values of the ELISA in units to analyze the possible correlations between age, IgE, and infection of the two most prevalent infections. Interestingly, only in the atopic and asthma groups were there significant correlations with age, IgE, and FEV1. There were correlations between the values recorded in units of parasite-positive IgG and IgE values only in the asthma group. No significant correlations were found in the control and COPD groups.

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Table 1. The characteristics of the cohort.

	CONTROL	ATOPIC	ASTHMA	COPD	P
n	100	100	100	100	ANOVA
AGE	41.13 ± 15.6	46.6 ± 16.9	50.2 ± 13.5	65.7 ± 7.0	>0.01
FEMALE (%)	57	54	58	56	0.9
SMOKERS (%)	0	10	10	75	>0.0001
$FVEF_1$ % pred	110.33 ± 6.8	102.9 ± 5.9	76.7 ± 12.3	58.8 ± 9.1	>0.0001
FEV1/FVC ratio	85.8 ± 4.5	80.6 ± 3.2	69.1 ± 11.9	53,6 ± 12,6	>0.0001
IgE (IU/ml)	68.2 ± 16.2	321.8 ± 150.8	199.4 ± 147.1	155.2 ± 129.3	>0.0001
% elevated IgE	0	89	61	39	>0.0001

Table 2. Hematological values of the different groups.

%	CONTROL	ATOPIC	ASTHMA	COPD	ANOVA
Lymphocytes	28.8±2.5	30.0±2.4	29.6±3.0	29.2±3.4	0.9
Neutrophils	63.6±3.0	56.0±4.4	54.4±3.2	59.4±2.1	>0.001
Monocytes	6.3±1.6	7.1±1.4	7.2±1.8	6.9±1.9	0.5
Eosinophils	1.3±1.2	7.0±1.5	5.7±4.3	4.6±3.0	>0.0001

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Table 3. The positiveness of the IgG against the different parasites.

	IgE	n	Al	Ss	Tc
CONTROLS	Normal	100	6*	0	0
ATOPIC	Normal	11	1*	0	0
	High	89	18*	0	4**

Table legend: * stool tests confirmed infection, ** IF and ELISA tests confirmed infection.

Al states for Ascaris lumbricoides, Ss Strongyloides stercolaris and Tc for Toxocara canis.

Table 4. Parasite infection, according to disease status.

ASTHMA		N	*Al*	*Ss*	*Tc*
	Severe	10	5	0	1
	Moderate	48	7*	0	5**
	Intermitent	28	0	0	0
	Mild	14	0	0	0
COPD	Severe	13	1	3	0
	Moderate	77	8*	1*	4**
	Mild	10	0	0	0

Table legend: * Stool tests confirmed infection, ** IF and ELISA tests confirmed infection.

Al states for Ascaris lumbricoides, Ss Strongyloides stercolaris and Tc for Toxocara canis.

Table 5. Correlations between parasite infection and FEV1.

Controls	FEV1	IgE	Al IgG values	Tc IgG values
Age	-0.31	-0.11	-0.01	-0.02
IgE	-0.02		-0.07	-0.11
Atopic				

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Age	**-0.64**	0.32	0.36	0.18
IgE	**-0.48**		0.32	0.08
Asthma				
Age	**-0.37**	-0.06	-0.02	-0.03
IgE	**-0.44**		**0.55**	**0.46**
COPD				
Age	-0.27	0.2	0.17	0.18
IgE	-0.16		0.06	0.32

The table represents the Pearson correlations encountered with the different categories analyzed in the cohort. Only significance was observed in the atopic and asthma groups.

4. Discussion

Patients with atopy, asthma, and COPD are complex patients since chronic disease predisposes them to several other medical conditions. Steroids, a common anti-inflammatory treatment, have generated an array of secondary events that have limited the scope of treatment. On the other hand, the assessment, diagnosis, and treatment of different obstructive diseases have changed over the last few years.

In tropical countries, especially in underdeveloped areas with high frequencies of parasitic diseases, it is difficult to find individuals who are not infected. We have identified three parasites that migrate to the lungs at some point in their life cycle. It is well known that *Strongyloides stercolaris* infection can persist in the host for a long time and that *Ascaris lumbricoides* may persist in immunosuppressed patients. The infection of *Toxocara canis* may be less common in elders and more common in toddlers who are in contact with puppies. On the other hand, toddlers may infect adults in the household. In all cases, lung migration upon or over-infection may be observed. This migration may increase susceptibility to inflammation and inflammation induced by allergens, cigarette smoke, or other gases. Several reports of increased susceptibility to long bronchoconstriction have been reported along with parasitic infection [16,19,22,27,36,37].

The study was composed of different groups. The control group of atopic individuals was included to analyze the possible role of these infections in FEV1. As expected, the IgE levels were high and can be considered an essential marker for analysis. Individuals with high IgE levels and atopic conditions showed no signs of lung obstruction, indicating that the Th2 pattern was only involved in the allergic reaction. Although IgE levels were correlated with FEV1 in the asthmatic group, they also appeared to be linked to the detected reactivity against parasites, suggesting a potential connection between these events. Some studies have sought to establish a connection between IgE levels and the severity of asthma symptoms, proposing that parasites may be responsible for the severity of bronchoconstriction. However, based on the results of our study, it is evident that the contribution of IgE is only partial, as demonstrated by the atopic group, where IgE levels were higher than in the asthmatic group.

Interestingly, there are no correlations of any parameters in COPD patients. There could be two reasons for this. First, age might make individuals less responsive to the allergen. Additionally, the anti-inflammatory treatment could reduce the response. Parasite infection may be confused with

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exacerbation in COPD. Toychiev A. et al. [38] conducted a study to examine the impact of *Ascaris lumbricoides* on the development of chronic pulmonary aspergillosis in patients with COPD. They discovered that the prevalence of *A. lumbricoides* in COPD patients with chronic pulmonary aspergillosis is high. Furthermore, the study found elevated levels of IL-1β and TNFα, indicating that ascariasis increases susceptibility to Aspergillus sp. in COPD patients.

Current guidelines for inhaled steroid treatment in COPD require blood eosinophil counts, which makes it essential to determine concomitant infection with these parasites in our COPD patients [3]. Steroids may facilitate parasite infection and progression, as was described in asthmatic patients [39]. Biological therapy may also be affecting the response [40]. There is an increased risk of parasite infection in different treatments [40,41]. This issue requires further research.

Since patients may probably be infected with at least one parasite, a routine screening is recommended. We cannot discard that some of the COPD patients had asthma-COPD overlap syndrome due to the increased amount of IgE and probably other allergic conditions that the treatment may mask.

Since our cohort patients were adults, it is difficult to determine whether atopic conditions that have persisted for a lifetime may be involved in other physiological responses. IgE has to play a role, and it will be important to establish how these cells may be important later in the life of a medical condition.

It is also essential to understand the rationale of the parasite infection if the infection is due simply to normal exposure and the lack of proper immune response due to the therapy in conjunction with the chronicity of the disease or if it is an independent factor. Since infection by *Ascaris* and *Strongyloides* may be long-lived without clinical manifestations, it is unclear if pharmacological treatment decreasing the parasite burden is sufficient to prevent or exacerbate a chronic inflammatory condition after the individual is reinfected. Antibodies may be a useful marker to define specific responses.

The presence of parasite infections may play a significant role in various chronic inflammatory conditions, potentially contributing to an increase in symptoms but not necessarily essential to the progression of the disease. Investigating the long-term effects of anti-parasitic treatment on these individuals would be valuable. Better control of parasitic diseases could improve patients' quality of life.

5. Conclusions

Ascaris lumbricoides infection is common in the Venezuelan population; however, it is more prevalent in atopic patients and moderate to severe patients with asthma or COPD. *S. stercolaris* infection is less frequent and only observed in this cohort of COPD patients. *T canis* IgG positiveness was observed in around 10 % of patients but not in controls. The higher incidence of parasite infection in patients may be due to partial to severe immune compromised responses, which may be due to treatment or other medical conditions, especially in COPD patients.

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Institutional Review Board Statement: The study was conducted following the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the Institute of Immunology, Faculty of Medicine, Universidad Central de Venezuela (protocol code HS101020205, date of approval 01/02/2005).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Appendix A contains the individual data of each patient, which is enclosed in the file.

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