The role of protozoa in the etiology of chronic urticaria

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ABSTRACT

Background: Urticaria is a condition characterized by short-lived swellings of the skin, mouth, and genitalia due to transient leakage of plasma from small blood vessels into the surrounding connective tissues. Although infectious agents such as bacteria and virus causing acute urticaria have been reported previously, very little research has been carried out to understand the relationship between parasitosis and urticaria. This study was designed to contribute to the understanding of the relationship between parasitosis and urticaria.

Methods: A total of 49 patients with chronic urticaria and 36 healthy participants were included in the study. Three stool samples were taken from each patient on different days before treating the patients with antiparasitic drugs. Fecal parasite concentrator and native Lugol's method were used for the microscopic examination of the stool samples. Stain samples were prepared by acid fast and modified trichrome staining methods. Serum immunoglobulin E (IgE) levels of both groups were measured using the nephelometric method.

Results: Our results revealed that protozoa were detected in 38.8% of patients and in 11.1% of healthy participants. There was a fourfold increase in the total serum IgE levels of patients detected with protozoa when compared with patients in whom protozoa were not detected.

Conclusion: In patients who have urticaria with undetectable etiology, stool parasite screening would be prudent and identification of parasite-specific IgE in patients with urticaria would be useful in defining the mechanisms by which the parasite causes these lesions.

* The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

Introduction

Urticaria is a condition characterized by short-lived swellings of the skin, mouth, and genitalia due to transient leakage of plasma from small blood vessels into the surrounding connective tissues. Deeper swellings of the dermis and subcutaneous and submucosal tissues are called angio-edema. When urticarial lesions persist for >24 hours, a diagnosis of urticarial vasculitis or delayed pressure urticaria should be considered. Some studies have demonstrated that about 0.1% of the population has urticaria, and that the cumulative prevalence rates vary between 15% and 25%. A classification based on clinical features is used to guide appropriate investigation and management. According to this classification urticaria is divided into the following two groups: ordinary urticaria (acute, chronic, episodic) and physical urticaria (mechanical, thermal, other). While urticaria is defined “acute” if it lasts for <6 weeks, chronic urticaria (CU) is defined as any pattern of recurrent urticaria occurring at least two times a week for at least 6 weeks. Pathogenic mechanisms that are responsible for the development of CU have been elucidated previously. Evidence of an autoimmune etiology in approximately 45% of patients has been presented and it continues to be an area of active investigation. Although reports on infectious agents such as bacteria and virus causing acute urticaria and their subsequent attacks during the course of CU have been published previously, very little research has been carried out to understand the relationship between parasitosis and urticaria. This study was designed to contribute to the understanding of this relationship.

Materials and methods

The study population included a random sample of patients between 23 and 63 years (mean: 46.1 ± 8.0) of age who presented to the Rize Education and Research Hospital of Turkey with symptoms suggesting CU of unknown etiology. The study was carried out with the permission of the local ethics committee of our
medical faculty. Patients who had an attack of CU were included in the study. However, patients who presented with a history of suspected drug use within the last week or with apparent signs of infection were excluded. Only 49 patients who fulfilled this inclusion criteria were considered for further analysis. The control group (n = 36) consisted of patients who were admitted in the hospital for general health control. Three stool samples were taken from each patient on different days before treatment with antiparasitic drugs. Stool samples taken from the patients and the control group were sent to the microbiology laboratory to be examined for the presence of parasites. Fecal parasite concentrator (Mini Parasep SF, England) and native Lugol’s method were used for the microscopic examination of the stool samples. Stain samples were prepared by acid fast and modified trichrome stain (ADR, Turkey) methods. Serum immunoglobulin E (IgE) levels were measured by the nephelometric method (Beckman Coulter IMMAGE 800 immunochemistry system) in both the patients group and the control group. All of the patients detected with parasitic infection were administered a dose of metronidazole (500 mg × 2/day) for a period of 10 days.

Statistical calculations created using the Statistical Pocket for Social Sciences (SPSS 11.0) program Chi-square test was used to compare the cases of CU with healthy controls in terms of frequency of the presence of protozoa.

Results

A total of 49 patients with CU were included in the study: 34 women (69.4%) and 15 men (30.6%) (Figure 1). Although the mean age of patients was 46 (46.1 ± 8.0), the mean age of the control group was 47 (mean: 46.7 ± 9.2; n = 36). Results of the examination of stool samples of the 49 CU cases revealed the presence of the following parasites: Entamoeba coli in nine cases, Blastocystis hominis in seven cases, and Giardia spp. in three cases. The total incidence of these protozoa in the patient group was determined in as 38.8%, whereas it was determined as 11.1% in the healthy control group (i.e., three for E. coli and one for B. hominis; n = 4) (Tables 1 and 2). A statistically significant difference was found between the patient group and the control group regarding the frequency of the presence of the parasites (Chi-square, p = 0.05).

The mean concentration of total serum IgE was 118.6 ± 87.1 in patients who tested positive for the various protozoa, whereas it was 33.5 ± 14.6 in patients who tested negative. Approximately fourfold elevation in serum IgE level was seen in patients infected with these protozoa. Mean concentration levels of total serum IgE were 98.5 ± 12.3 and 30.8 ± 17.0 in the control group, protozoa-positive and protozoa-negative groups, respectively. CU remissions were found in eight of the 19 patients (42%) who had parasitic infestation after treatment. Metronidazole-treated patients were followed up 1 month later. As a result of follow-up, parasitic infestation was detected in the five of the 19 cases (26%).

Discussion

Parasites colonize the human gastrointestinal tract and often coexist harmoniously with their host. Asymptomatic carriage is the most common form of intestinal parasitic infection worldwide. The kinds and incidence of intestinal parasites vary between different regions of the world. These infections are the result of inter-related social, economic, cultural, historical, and political factors. Some of the protozoa may cause extra-intestinal manifestations, such as urticaria. Even though intestinal parasites are often mentioned as a possible cause of urticaria, very few studies have been carried out regarding this and no experimental papers concerning the role of intestinal parasites in CU have been published. Laboratory and clinical investigations greatly vary from one center to another. Although several different hypotheses have been suggested, the mechanisms by which parasites could stimulate the clinical expression of allergic reactivity are not fully understood. Therefore, clinical observations may help to identify possible links between intestinal parasites and hypersensitivities. In patients with unexplained eosinophilia and a relevant history of travel abroad, fresh stool samples can be sent for detection for the presence of cysts, ova, and parasites. Serology may be an alternative investigation in some cases. Giardia lamblia, Entamoeba spp., and Blastocystis spp. have been suspected to trigger urticarial symptoms in patients with chronic spontaneous urticaria.

Six species of the genus Entamoeba, i.e., E. histolytica, E. dispar, E. moshkovskii, E. polecki, E. coli, and E. hartmanni can be found in human stools. Of these species, only E. histolytica is considered to be pathogenic, causing intestinal and extra-intestinal diseases. Nevertheless, all Entamoeba spp. should be reported in parasitological examination of stool samples. In our study, E. coli was the major parasite detected in the stools of the patient group and the control group. The other two parasites detected in our study are B. hominis and G. lamblia. Both these parasites have previously been reported in various studies. In fact, in one of the previous studies that was carried out in patients with CU (n = 46 patients), about 35% of the parasites discovered were B. hominis. E. coli is the most frequently detected protozoan in our study. This difference may be due to regional differences. Statistically significant difference was observed between the patient group and the control group regarding the frequency of the parasite present in our study.

Table 1 Frequency of presence of protozoa in the patient group and the control group.

<table>
<thead>
<tr>
<th>Parasite detection</th>
<th>Patient group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Negative</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>36</td>
</tr>
</tbody>
</table>

Table 2 Types of protozoa isolated from the patient group and the control group.

<table>
<thead>
<tr>
<th>Protozoa</th>
<th>Patient group, n (%)</th>
<th>Control group, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entamoeba coli</td>
<td>9 (18.3%)</td>
<td>3 (8.3%)</td>
</tr>
<tr>
<td>Blastocystis hominis</td>
<td>7 (14.3%)</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Giardia spp.</td>
<td>3 (6.3%)</td>
<td>ND</td>
</tr>
<tr>
<td>Total</td>
<td>19 (38.8%)</td>
<td>4 (11.1%)</td>
</tr>
</tbody>
</table>

n = number, ND — not detected.
(Chi-square, \( p \leq 0.05 \)). We believe that the results of our study were not affected by the differences in socio-economic class owing to the presence of wide social medical network in our country. Statistically significant difference between the patient group and the control group for the presence of parasite and CU remissions after treatment in some of the patients suggest that parasitic infections can play a role in the etiology of urticaria. Detection of parasitic infestation after treatment in our study suggests that CU remissions rate may be affected by metronidazole resistance.

In an effort to understand the relationship between parasites and urticaria, some researchers think that possible antigens of \( B. \) hominis might cause inflammatory cell recruitment, which release histamine-activating factors that prime mast cells and basophils. In addition, IgE might also be a possible mediator in urticaria through mast cell activation and degranulation.\(^{25}\) In 1966, Ishizaka et al. started a new era in the pathophysiology of immunological disorders when they identified and purified IgE from the serum of allergic patients. Human IgE molecules bind to receptors (FcεRI) on the surface of human basophils and mast cells. IgE cross-linking results in the release of a variety of preformed (\( e.g., \) histamine) and de novo-synthesized chemical mediators (\( e.g., \) peptide leukotrienes, prostaglandins) and cytokines.\(^{26}\) Studies that followed showed that at least 30% of patients with chronic “idiopathic” urticaria have histamine-releasing autoantibodies that degranulate mast cells and basophils by binding high-affinity IgE receptors or IgE bound to them.\(^{27,28}\) The etiology in the remaining patients is unknown and this group remains idiopathic.\(^{30}\) Although the relationship between elevated levels of total serum IgE and CU has been detected in one study, it was not detected in another study that was recently published.\(^{28,29}\) Parasitic infections can cause a 10- to 100-fold elevation in total serum IgE levels. These infections not only stimulate the production of specific antiparasite IgE, but also nonspecifically induce polyclonal IgE synthesis.\(^{30}\) In our study, similar IgE levels were found in the individuals who tested negative in both the patient group and in the control group. However, individuals who tested positive in the patient group and in the control group showed increased levels of IgE.

In the light of our findings, we believe that stool parasite screening would be advisable for patients who have urticaria with undetectable etiology. Increased levels of IgE may suggest parasitic infections but identification of parasite-specific IgE in patients with urticaria would be useful in defining the mechanism by which the parasite causes these lesions.

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