





Original Article

Intestinal parasitic infestations in adult chronic spontaneous urticaria patients and the relation between them: A case-control study

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ABSTRACT

Objectives: Chronic urticaria (CU) is a prevalent allergic skin condition with variable symptoms and a complex etiology. It is characterized by the presence of itchy hives, angioedema, or both on at least twice-weekly basis for more than 6 weeks. The cause of CU has yet to be thoroughly established. It is unclear how intestinal parasites affect CU and whether they can trigger the clinical manifestations of allergic reactions. The study aimed to assess the prevalence of intestinal parasitic infestations in adults with chronic spontaneous urticaria (CSU) and explore their potential association.

Material and Methods: This was a case-control study that included 100 healthy individuals as group control and 100 patients suffering from CSU. All patients were examined for stool analysis to detect intestinal parasitic infestations.

Results: The age of patients ranged from 20 to 57. The prevalence of intestinal parasitic infestations was 66% in the CSU patients, which was statistically significantly higher as compared to the control group (16%) ($P < 0.001$). There was a strong relationship between positive parasitic infestations and the severity of urticaria. There was a higher rate of positive parasitic infestations in the cases that did not respond to the full dose of antihistamine and needed a second line of treatment (92.9%) as compared to the cases treated only with antihistamine (55.6%) ($P < 0.001$).

Conclusion: The prevalence of intestinal parasitic infestations was higher in CU patients and also correlated with its severity.

Keywords: Intestinal parasitic infestations, Prevalence, Severity, Urticaria

INTRODUCTION

Urticaria is an allergic reaction characterized by smooth, edematous, erythematous, and itchy wheals. Usually, it lasts <24 h without post-inflammatory hyperpigmentation. Urticaria is classified as acute or chronic, depending on its duration. This condition is thought to affect at least 0.5–5% of the population. The possible causes of chronic urticaria (CU) are infections, dental caries, parasitic infestations, some types of food, thyroid diseases, and drugs.^[1,2] CU is a debilitating disorder that severely reduces the quality of life and has a considerable impact on the healthcare systems.^[3]

Chronic spontaneous urticaria's (CSU) etiology is not yet fully understood. Mast cells and basophils, whose activation and degranulation cause histamine release, have been implicated. Mast cells also release cytokines and chemokines that are responsible for attracting the perivascular infiltration seen around tiny venules in the skin of CSU patients. CSU is hypothesized to be driven by autoimmunity, involving immunoglobulin (Ig)G and IgE autoantibodies as well as

high-affinity IgE receptors. However, only a small proportion of patients satisfy all the criteria for autoimmunity.^[4] Parasitic infestations were first hypothesized as an underlying cause in a pediatric CSU patient with *Giardia lamblia*, but the role of parasites in the etiology of CSU and the pathogenic mechanisms were unclear.^[5,6] The objectives of this study were to detect the prevalence of intestinal parasitic infestations in patients suffering from CSU and evaluate the correlation between them.

MATERIAL AND METHODS

This was a case-control study with 100 consecutive patients suffering from CSU who sought treatment at our urticaria and immunity unit and 100 healthy individuals as group control who sought treatment at outpatient cosmetic and laser clinics of Cairo Hospital of Dermatology and Venereology. All patients were examined for stool analysis to detect intestinal parasitic infestations. The study received approval from the Training and Research Sector in the Ministry of Health and Population (Ethical Committee No: 20-2023/12) and was conducted from

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May 2023 to March 2024. The included cases were told about the goal of the investigation and informed written consent was obtained from the patients before enrollment in this study. Inclusion criteria were adults aged 20–60 years, of both sexes, diagnosed with CSU whereas, exclusion criteria were pregnant or lactating women and individuals with a history of malignancies. The sample size was calculated using the formula, $n = Z1-\alpha^2 P(1-P)/d^2$, where n is the sample size, Z is 1.96 (with a 95% confidence level), and P is the predicted prevalence of intestinal parasite infestations in patients with urticaria = 0.145 (14.5%) according to the results of a systematic review study done by Kolkhir *et al.*, 2016,^[7] and d = precision (margin of error) = 7% (0.07). Patients were asked about their age, gender, onset, course, and duration of CU, as well as any concomitant conditions and drug history. A general examination for signs of systemic disease and local examination for assessing the severity of urticaria by calculation of urticaria total severity score was carried out. The total severity score for urticaria was computed by adding six parameters: the number of wheals, the size of the wheals by measuring with a ruler, the intensity of the pruritus, the duration of the persistence of symptoms, the frequency of appearance, and the frequency of antihistamine usage (all patients were treated according to the European Academy of Allergy and Clinical Immunology [EAACI] guidelines). Each parameter's score ranged from zero to three. Urticarial disease severity was graded as clear (0), mild (1–6), moderate (7–12), or severe (13–18) [Table 1].

Laboratory investigation

Stool analysis was done for 100 healthy individuals as group control and 100 patients suffering from CSU. Fresh stool samples from patients and controls were obtained and sent to the laboratory within 30 min. Each patient provided a fresh, fixative-containing stool sample (10% formalin solution). Following macroscopic examination, new feces samples were analyzed through direct microscopy (saline and iodine) and Wheatley's trichrome staining. Fixative-containing stool samples were concentrated using the stool concentration method (Parasep® Fecal Parasite Concentrators, Apacor, USA), and sediments were analyzed as wet mounts in saline and iodine for intestinal parasites.

Statistical analysis

The collected data were edited, categorized, and calculated using the IBM Corp. Statistical Program for Social Science (released in 2017). IBM Statistical Package for the Social Sciences Statistics for Windows, Version 25.0 (Armonk, New York: IBM Corp.). Appropriate analysis was carried out based on the type of data obtained for each parameter. The degree of significance was assessed and given as the likelihood of (*P*-value).

RESULTS

This was a case-control study that included 100 healthy individuals as group control and 100 patients suffering from CSU. The mean age in the case group was 36.91 ± 10.47 years and the mean age in the control group was 35.94 ± 10.54 years, with no statistically significant difference between the two groups (*P* = 0.515). There were 39% males and 61% females in the case group, while there were 45% males and 55% females in the control group, with no statistically significant difference between the two groups (*P* = 0.390) [Table 2]. In the case group, the mean urticaria duration was 15.1 ± 11.7 months with a range between 3 and 48 months. The urticarial severity was classified as mild, moderate, and severe in 26%, 49%, and 25%, respectively.

Parasitic infection

The prevalence of parasitic infestations in the stool was 66% in the case group, which was statistically significantly higher as compared to the control group (16%) (*P* < 0.001) [Table 3]. There was no statistically significant difference between the cases with parasitic infestations regarding age and sex. Regarding the type of parasite isolated, there was no statistically significant difference between the two groups (*P* = 0.346), with *Entamoeba histolytica* the most common type of helminth isolated; observed in 94% and 87.5%, respectively. Significantly, 62 of 66 patients with CSU (94%) had *E. histolytica*. The other parasites that grew included, *Blastocystis hominis* 2%, *Giardia intestinalis* 1%, and *Dientamoeba fragilis* 1% [Table 4]. There was no statistically significant difference between the cases with different urticarial severity regarding the type of parasitic infestations [Table 5]. However, there

Table 1: Urticaria total severity score.

Parameters	Scores			
	0	1	2	3
Number of wheals	None	<=10	11-50	>= 50
Size of wheals	None	<1 cm	1-3 cm	>3
Intensity of pruritus	None	Mild	Moderate	Severe
Duration of persistence of symptoms	None	< 1 h	1-12 h	>12 h
Frequency of appearance	None	<Once or once a week	2-3 times a week	Daily/almost dally
Frequency of antihistamine	None	<Once or once a week	3 times a week	Daily/almost daily

Table 2: Comparison of the demographic data in the two study groups.

	Groups		Test of significance	P-value
	Case group (n=100)	Control group (n=100)		
Age (Years)				
Mean±SD	36.91±10.47	35.94±10.54	t=0.653	0.515
Range	20–57	20–55		
Sex (%)				
Male	39 (39)	45 (45)	$\chi^2=0.739$	0.390
Female	61 (61)	55 (55)		

P: Probability, SD: Standard deviation. Quantitative data expressed as mean±SD/range, Categorical data expressed as Number (%), χ^2 : Chi-square test/t: Independent samples *t*-test

Table 3: Comparison of the stool results of the parasitic infestations in the two study groups.

	Groups (%)		Test of significance	P-value
	Case group (n=100)	Control group (n=100)		
Parasites infestations				
Absent	34 (34)	84 (84)	$\chi^2=51.647$	<0.001*
Present	66 (66)	16 (16)		

P: Probability. Categorical data expressed as Number (%), χ^2 : Chi-square test, *: Significant *P*-value (<0.05)

Table 4: Comparison of type of parasitic infestations among affected patients in two study groups.

	Groups (%)		Test of significance	P-value
	Case group (n=66)	Control group (n=16)		
Type of positive parasite infestations				
<i>Entamoeba histolytica</i>	62 (94)	14 (87.5)	MC=1.874	0.346
<i>Blastocystis hominis</i>	2 (3)	1 (6.25)		
<i>Giardia intestinalis</i>	1 (1.5)	1 (6.25)		
<i>Dientamoeba fragilis</i>	1 (1.5)	0 (0)		

P: Probability. Categorical data expressed as Number (%), MC: Monte–Carlo test

Table 5: Relation between the severity of the urticarial disease and the type of parasitic infestations in affected patients in the case group (cases with positive parasitic infestations).

	Mild (%) (n=1)	Moderate (%) (n=42)	Severe (%) (n=23)	Test of significance
Type of parasitic infestations				
<i>Entamoeba histolytica</i>	1 (100)	39 (92.8)	22 (95.7)	MC=1.962 P=0.284
<i>Blastocystis hominis</i>	0 (0)	1 (2.4)	1 (4.3)	
<i>Giardia intestinalis</i>	0 (0)	1 (2.4)	0 (0)	
<i>Dientamoeba fragilis</i>	0 (0)	1 (2.4)	0 (0)	

P: Probability. Categorical data expressed as Number (%), MC: Montecarlo test, *: Significant *P*-value (<0.05)

was a higher relationship of positive parasitic infestations in the cases with severe (92%) and moderate (85.7%) urticarial

diseases as compared to the mild cases with mild severity (3.8%) (*P* <0.001) [Table 6].

As per EAACI guidelines, all patients were treated with antihistamines with 72% of the cases responding to antihistamines while 28% of them did not respond to antihistamines and needed a second line of treatment. Interestingly, there was a strong relationship between positive parasitic infestations in the cases that did not respond to the full dose of antihistamine and where a second line of treatment (92.9%) was needed as compared to the cases that responded to antihistamine only (55.6%) ($P < 0.001$) [Table 7].

DISCUSSION

CU is a multifaceted inflammatory skin illness caused by the activation and degranulation of cutaneous mast cells, followed by the release of histamine and other mediators that cause sensory nerve stimulation, vasodilation, plasma extravasation, and cellular recruitment. This mechanism induces the development of the disease-defining signs and symptoms, itchy hives, and angioedema (or both).^[7,8] Although urticaria is a widespread condition, its pathophysiology is poorly known. It is also unclear how intestinal parasite infections affect CU and whether they might cause clinical signs of allergic reactions. Clinical observations may assist in discovering probable correlations between intestinal parasite infections and hypersensitivities.^[9] Our goal, based on this evidence, was to determine the prevalence of intestinal parasitic infestations in adult patients suffering from CU. This was a case-control study with 100 healthy individuals as the group control and 100 patients suffering from CU as the case group. In the current study, the age of the studied population ranged from 20 to 57 years, the mean age in the case group was 36.91 ± 10.47 years, and the mean age in the control group was 35.94 ± 10.54 years. Most research indicates that the peak

age of CU occurrence is between 20 and 40 years. Therefore, patients are primarily affected during their working years and are more prone to absence and lower productivity due to the sickness and its treatment.^[10] A Spanish study found that the average age of patients was 35.75 ± 18.9 years, which is nearly similar to ours.^[11]

Urticaria can affect both sexes, but females are roughly twice as likely as males to develop it.^[12] This was in accordance with our results where we found the predominance of the female gender to be nearly twice the male gender (female [61%], and male [39%]), concurrent with what has been reported in previous studies.^[13-15] In contrast, Ban *et al.*, discovered a lack of female predominance in the elderly CU group, despite a 57.9% prevalence of females in the overall study population.^[16] This finding is in concordance with a previous report of an almost equal sex distribution in an elderly CSU group.^[17]

The present study showed that in the case group, the mean urticaria duration was 15.1 ± 11.7 months with a range between 3 and 48 months. Dias *et al.* discovered that the mean time for illness progression was 10.6 years (3 months–60 years).^[18] In the study by Baiardini *et al.* the duration was shorter, approximately 1 year and 9 months.^[19] Gaig *et al.* discovered that 50% of CU patients were asymptomatic after 3 months and 80% after 12 months. However, 11% had affliction for over 5 years.^[20]

In the current research, the severity of urticaria was classified as mild, moderate, and severe in 26%, 49%, and 25%, respectively. This was consistent with the ASSURE trial, which revealed that almost 70% of patients had moderate-to-severe CSU, with an average urticaria duration of 5 years.^[21] Further, Ye *et al.*, showed that the overall disease duration of CSU was roughly 4 years, with nearly half of patients classified as having moderate-to-severe CSU.^[22]

Table 6: Relation between the severity of the urticaria and the prevalence of parasitic infestations in the case group.

	Mild (%) (n=26)	Moderate (%) (n=49)	Severe (%) (n=25)	Test of significance
Parasite infestations				
Absent	25 (96.2)	7 (14.3)	2 (8)	MC=60.777 P<0.001*
Present	1 (3.8)	42 (85.7)	23 (92)	

P: Probability. Categorical data expressed as Number (%), MC: Monte-Carlo test, *: Significant P-value (<0.05)

Table 7: Relation between type of treatment and parasitic infestations in the case group.

	Respond to antihistamine (n=72) (%)	Not respond to antihistamine and needs a second line of treatment (n=28) (%)	Test of significance	P-value
Parasite infestation				
Absent	32 (44.4)	2 (7.1)	FET=12.500	P<0.001*
Present	40 (55.6)	26 (92.9)		

P: Probability. SD: Standard deviation. Quantitative data expressed as mean±SD/range, Categorical data expressed as Number (%), χ^2 : Chi-square test/t: Independent samples t-test. *: Significant P-value (< 0.05). FET: Fisher's exact test

In this study, all patients were treated according to the EAACI guidelines.^[23] This guideline suggests the use of second-generation H1 antihistamines as the first line of treatment. Antihistamine use resulted in 72% of the cases responding, while 28% of them did not respond to antihistamines and needed a second line of treatment.

The present study showed that the prevalence of intestinal parasitic infestations in the stool was 66% in the case group which was statistically significantly higher as compared to the control group (16%) ($P < 0.001$). In line with our findings, Dhanabal *et al.* reported that the prevalence of intestinal parasitic infestations was 75.8% (194 of 256 stool samples were positive); and *Entamoeba coli* (23%), *Cyclospora* spp. (22.2%), *E. histolytica* (21.8%), *G. intestinalis* (14.4%), and *Ascaris lumbricoides* (6.2%) were the most prevalent parasites.^[24] However, in our research, *E. histolytica* was the most common parasitic infestation in CSU patients.

The prevalence of intestinal parasitic infestations in the present study was comparable to a previous study that was conducted in India and reported the prevalence of intestinal parasitic infestations ranged from 33% in urban patients as compared to 91% in rural patients.^[25] In a Turkish study, parasitic infestations were discovered in 38.8% of the CSU patients and 11.1% of the control group, with a statistically significant difference between the groups.^[4] In another study with 55 CSU patients, *Blastocystis* spp. was isolated in 20% of the patients and 11.6% of the controls, and the difference between the groups was found to be statistically significant.^[6] Vezir *et al.* determined that the prevalence of intestinal parasitic infestations was 18.4% and 22.3% of adult and pediatric CSU patients, respectively, with *Blastocystis* spp. being the most prevalent parasite, consistent with previous observations.^[26]

The current study revealed that there was no statistically significant difference in age, sex, and disease duration between the cases with different urticarial severity. Contrary to our result, Metin *et al.*, observed that longer urticarial disease duration and positive autologous serum skin test were present in patients with more severe CSU.^[27]

This study showed a statistically significant higher rate of positive parasitic infestations in the cases that did not respond to a full dose of antihistamine and needed a second line of treatment (92.9%) as compared to the cases that responded to antihistamine only (55.6%) ($P < 0.001$). In a double-blind crossover study, Kosnik and Subic reported that the subgroup with severe urticarial disease antihistamine resistance was more likely to benefit from the addition of montelukast.^[28] Alkeraye and AlRuhaimi further demonstrated that montelukast is a viable therapy choice for people with CU who are not properly controlled with antihistamines.^[29]

Clinical implication

- The present study demonstrated that 66% of the studied patients were positive for parasitic infestation, while it was 16% in the control group
- *E. histolytica* represented the most common parasite among the studied patients with a percentage of 94%, which may have a role in the exacerbation of urticarial symptoms, and its eradication may improve a considerable number of infected urticaria patients
- Positive parasitic infestations showed a higher prevalence in severe urticarial cases (92%) as compared with moderate (85.7%) and mild ones (3.8%)
- Cases that did not respond to antihistamine treatment showed a higher prevalence of parasite infestation (92.9%) as compared to the cases with antihistamine treatment only (55.6%).

Recommendation

1. Further studies with a large number of cases should be conducted to confirm our results
2. Further studies should be conducted to evaluate the effect of antiparasitic treatment in the management of CSU.

CONCLUSION

In light of our findings, we believe that stool parasite screening would be advisable for patients who have urticaria with undetectable etiology. Therefore, patients of CSU should have stool analysis as a routine investigation, especially in severe cases or with poor response to antihistamine treatment.

Ethical approval: The research/study was approved by the Institutional Review Board at the Training & Research Sector in the Ministry of Health & Population, number Ethical Committee No: 20-2023/12, dated April 2023.

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