

Urinary Tract Infection in Spontaneous Urticaria among Thi-Qar Patients

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Abstract

Urticaria is a common worldwide disease characterized by local transient skin or mucosal edema (wheal), deeper tissues involvement (angioedema), or both. It is classified into acute (initially) and chronic (after 6 weeks' duration); and into spontaneous (symptoms occur spontaneously) or inducible (in response to specific stimuli). Occasionally, infections are blamed as an underlying cause; of them are urinary tract infections (UTIs). An equal number (465) of urticaria patients and their age-sex matched controls were evaluated for presence of UTIs in a case-control observational study. Pyuria was found in (19.8%) of urticaria patients and (7.7%) of controls; while urine culture was positive in (8.2%) of urticaria patients and (2.4%) of controls. Association of urticaria with both pyuria and positive culture results were highly significant (p value < 0.001).

Keywords: *spontaneous urticaria, urinary tract infections, urinalysis, pyuria, case-control study.*

Introduction

Urticaria is characterized by local transient skin or mucosal edema (wheal), deeper tissues involvement (angioedema) or both^(1,2).

It is a common worldwide disease with lifetime prevalence ranging from around 8% to 22%^(1,3,4), with detrimental effect on quality of life measures (both objective functioning and subjective well-being).²

Different classification schemes of urticaria exist.

According to duration, urticaria is classified into acute and chronic^(2,4). Acute urticaria last less than 6 weeks while episodes of daily or almost daily wheals or angioedema lasting for 6 weeks or more are designated as chronic urticarial⁽²⁻⁴⁾. There is no qualitative difference between acute and chronic spontaneous urticaria, but acute forms tend to be more severe¹. However, we

should notice that all urticarias are acute initially with some (about 20% to 45%) become chronic after a period of time (i.e. 6 weeks)³. According to clinical behavior, urticaria can be classified into spontaneous (symptoms occur spontaneously) or inducible (in response to specific stimuli such as physical stimuli)^(1,3-5). This classification (rather than etiology based) is regarded the most practical when defining groups of patients, since etiology of urticaria at time of first consultation is often unknown^(2,3). Spontaneous urticaria (ordinary urticaria) include acute, intermittent (episodic), and chronic (idiopathic) subtypes, while inducible urticaria encompass physical and contact urticarias^(3,5). Urinary tract infections (UTIs) refer to growth of microorganisms (mostly bacteria) within the urinary tract. They are considered the commonest bacterial infection, though incidence is difficult to be accurately assessed since they are not reportable diseases⁶. The gold standard for the diagnosis of a UTI is the detection of the pathogen, in the presence of clinical symptoms, by urine culture (using midstream urine)⁷. Pyuria is the presence of an increased number of polymorphonuclear leukocytes in the urine (generally >10 WBC/HPF)^(8,9). It is evidence for genitourinary tract inflammation, not necessarily UTI, and being just present is not an indication for

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treatment. Lack of pyuria, however, is strong evidence UTI is absent^(8,9,14).

Methodology

Patients and Method: An age and sex-matched case-control observational analytic study arranged over a period of 2 years (since January 2017 till March 2019) to evaluate the association between urticaria and urinary tract infections.

Patients with clinical diagnosis of spontaneous urticaria was recruited from those with various types of urticaria attended specialist day clinics in 2 general hospitals and 4 specialist private dermatology clinics at Thi-Qar province in south of Iraq.

Each patient was evaluated by dermatologist to exclude patients with inducible urticaria, urticariavasculitis, and known urticarial drug reactions. All patients diagnosed as spontaneous “ordinary” urticaria, who agreed to be involved in study, were included. Repeated cases taken once.

Control group was selected randomly from patient attending these clinics who were not complaining from urticaria nor presented primarily for genitourinary complaints. Care was performed in this selection to match, whenever possible, proportions of study group regarding age, sex, and known influential factors such as pregnancy and diabetes mellitus.

Verbal consent was taken from each in both groups and extra cost was added on regarding investigation.

Data regarding age, sex, marital status, pregnancy, diabetes mellitus, were recorded and, whenever applicable, every patient was interrogated about symptoms of urinary tract infection i.e. urinary frequency, urgency, dysuria, new onset hematuria, suprapubic pain). They were examined for suprapubic and/or costovertebral tenderness, and for fever.

After carefully instructing patient regarding washing the area with soap and water and passing first part of voided urine, a clean mid-stream urine sample was collected using the commercially available sterile wide mouth leak proof 5 ml container and submitted directly (as early as possible) to the laboratory for analysis.

Initial rapid urine leucocyte esterase test was done using a test strip (Dipstick), and pyuria was regarded positive when leucocyte esterase test was positive.

Ten ml of urine sample was centrifuged for 5 minutes at 1500 rpm, 9.5 ml of supernatant was decanted, deposit was suspended and examined microscopically for presence of RBC, WBC, epithelial cells, cast, crystals, and bacteria.

White blood cell was expressed as cells per high power field (WBC/HPF), and pyuria was considered positive when number exceeds 10 (WBC/HPF).

Urine samples revealing high count of squamous epithelial cells (> 20/HPF) were regarded contaminated and urine sampling repeated with extra careful instructions regarding methodology.

Urine specimens with pyuria were inoculated on blood agar and MaConckey agar plates and incubated at 37C° for 24hours. The single pure isolated colony, when present, was transferred to nutrient agar medium for preservation and to carry out other tests. Positive cultures were recorded.

All data were tabulated, cleaned, edited and entered “IBM SPSS Statistics” program version 25 for analysis. Pearson Chi-Square Independence test (χ^2) was employed to assess the association. *P* value <0.01 were considered statistically significant.

Results

A total of 465 patients with clinical diagnosis of urticaria, which was regarded as non-inducible (i.e. spontaneous), was recruited for study.

Their age ranged from 3 to 77 years with a mean age of 35.74 (\pm SD 17.450) years. Regarding the control group (No.=465) their age ranged from 3 to 75 years with a mean age of 35.21 (\pm SD 17.234) years. Distributions, regarding the age group, were comparable. (Table 1).

Table 1: Distribution of both urticaria and control groups according to age.

Age (Year)	Urticaria Group		Control Group	
	No.	Percent	No.	Percent
1-10	57	12.3	59	12.7
11-20	29	6.2	30	6.5
21-30	70	15.1	70	15.1
31-40	117	25.2	116	24.9
41-50	98	21.1	101	21.7
51-60	52	11.2	50	10.8
61-70	33	7.1	32	6.9
71-	9	1.9	7	1.5
Total	465	100.0	465	100.0

Females constituted majority with 322 (69.2%) patients in the study group leaving males with 143 (30.8%) patients. Comparable figures are found in control group: 324 (69.7%) patients and 141 (30.3%) patients for females and males respectively.

Pyuria was regarded positive in 92 (19.8%) patients of the urticaria group, while it was found only in 36 (7.7%) of the control group. (Figure 1).

A highly significant association between urticaria and pyuria was observed, ($\chi^2(1) = 28.410, p < 0.001$). (Table 2).

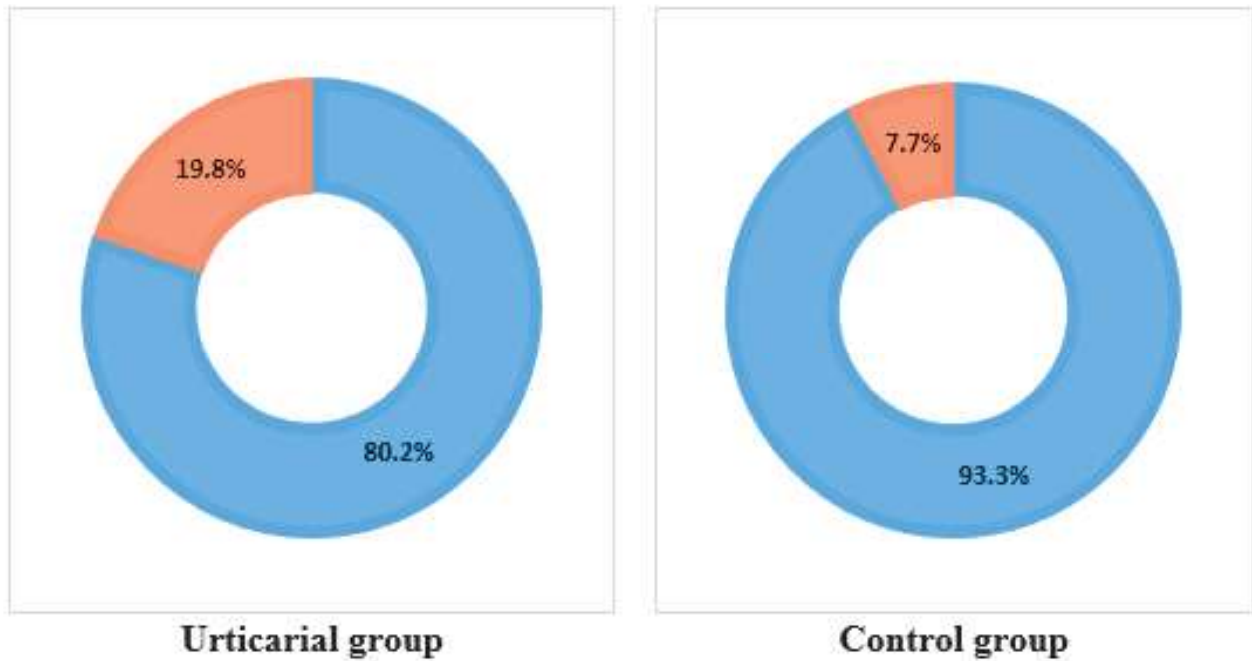


Figure 1: Pyuria distribution in both groups

Table 2: Association between urticaria and pyuria (Chi-Square Tests)

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	28.410	1	.000		
Continuity Correction	27.405	1	.000		
Likelihood Ratio	29.262	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	28.380	1	.000		
N of Valid Cases	930				

Positive urine culture results were obtained from 38 (8.2%) patient in the urticaria group, while such results were found in 11 (2.4%) urine samples from the control group. (Figure 2).

The association between urticaria and positive urine culture was a highly significant association, ($\chi^2(1) = 15.705, p < 0.001$). (Table 3).

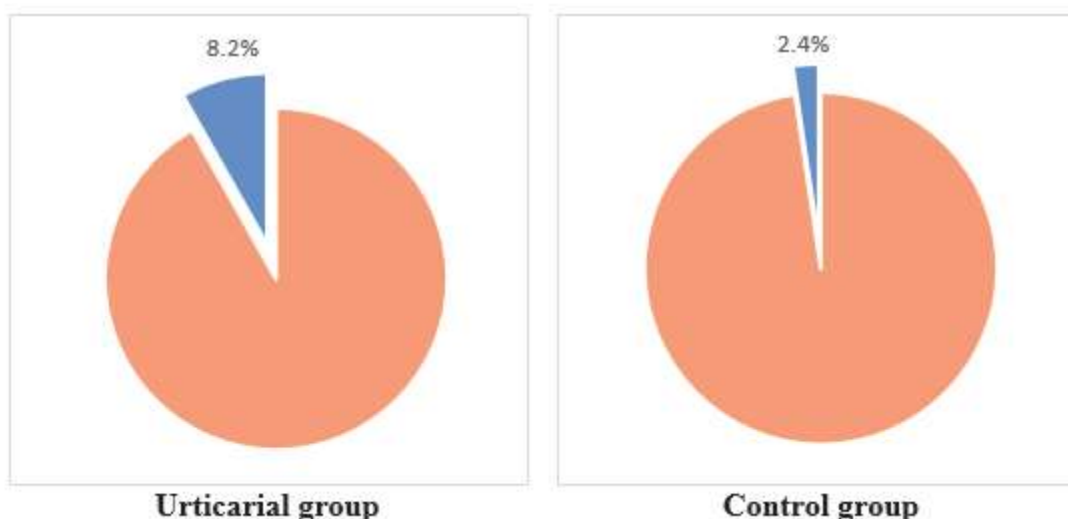


Figure 2: Positive urine culture distribution in both groups

Table 3: Association between urticaria and positive urine culture (Chi-Square Tests)

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	15.705	1	.000		
Continuity Correction	14.563	1	.000		
Likelihood Ratio	16.568	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	15.688	1	.000		
N of Valid Cases	930				

Regarding symptoms attributed to urinary tract infections: out of 92 urticaria patients with pyuria, 30 (32.6%) patients denied any such symptom. Out of 38 patients with positive urine culture, 11 (28.9%) revealed same negative symptomatic history.

Pregnant females constituted 12 from those 30 asymptomatic pyuria, and 5 of the 11 asymptomatic positive urine culture subgroups.

Regarding the isolated pathogens in positive culture results, these were dominated, in the urticaria group, by *Escherichia coli* which found in 20 (52.6%), followed by *Staphylococcus aureus* In 9 (23.6%), *Pseudomonas Spp.* In 5 (13.1%), *Klebsiella Spp.* In 3 (7.8%), then *Proteus* in 1(2.6%). In the control group, *Escherichia coli* was found in 7 (63.6%), followed by *Staphylococcus aureus* In 4 (36.6%), and *Pseudomonas Spp.* In 2 (18.1%).

Discussion

Association between infections (bacterial, viral, parasitic, or fungal) and ordinary (spontaneous) urticaria

(acute or chronic) has been noted long before, as early as in the 1920ies^(3,10,11). Their role had been discussed and included in most reviews¹¹, Never the less, proving a cause and effect relationship is often difficult, and inappropriate “blaming” a condition for causing urticaria may occur³.

Nearly all of the numerous studies reporting evidence for infectious agents triggering urticaria are case reports or retrospective observational studies without appropriate controls.¹² The relevance and frequency of infectious diseases varies between different patient groups and different geographical regions^(1,4,6). Urinary tract infection has been reported in number of publications as a cause in both acute and in chronic spontaneous (less in inducible) urticaria and angioedema¹⁰. As far as there is no possibility to challenge the patient with the suspected pathogen, thus making definitive recommendations regarding the role of infection in urticaria needs more research^(2,10).

Urinary tract infection, remarked initially by pyuria

and positive leukocyte esterase test was frequently noted to be found in cases of urticaria attending our clinics. The current study was arranged to test the substantial role and the “weight” of this association which, as we thought, did not receive the deserved attention in available studies.

Over period of 2 years we were able to collect a cohort of 465 patients with acute and chronic urticaria, which could be regarded as a reasonable sample of patient that get over many epidemiologic studies^(2,6,10,12) and enable studying the demographic characters of urticaria among our community.

Females (322 patients) outnumber males (143 patients) with a ratio of 2.2:1. Most epidemiologic studies reported similar predominance of females with variable ratios⁽¹⁻⁶⁾, though some excludes acute urticaria and extremes of age from this female predominance³.

Age groups affected were dominated by third to fifth decade, this may in part be due to more tendency to consult earlier in those age groups. So that many cases of urticaria that develop on just a single or a few occasions diminish within a week may be overlooked and not included. Most studies reported such peak age between 20 and 40 in chronic spontaneous urticarial^(1,6). When all types of urticaria were surveyed, a bimodal age distribution in patients aged birth to 9 years and 30 to 40 years was revealed^(1,3). acute spontaneous urticaria (along with urticarial reactions) may represent the first peak¹.

The term pyuria literally means “pus in the urine” but, in common usage, the focus is not on the presence of pus but on the number of white blood cells (WBCs) or amount of leukocyte esterase (LE) that exceeds a threshold and suggests a urinary tract infection (UTI)^(8,9).

Pyuria was detected (both by urine microscopy and by leukocyte esterase test) in 92 (19.8%) patients of the urticaria group, while it was found only in 36 (7.7%) of the control group. Statistical analysis of the two rate values revealed a highly significant association (with a p value < 0.001) between urticaria and pyuria.

Using evidence of inflammation (pyuria) in the urine to screen for who needs a culture seems justified on the basis of practicality at point of care and likelihood of UTI^(9,13). The absence of pyuria is a strong indicator that a UTI is not present and is useful in ruling out a UTI^(8,9,14).

Also If there are, in fact, some true UTIs without evidence of inflammation from the urinalysis, are they as harmful as those with “pyuria”? Animal data demonstrate it is the inflammatory response, not the presence of organisms, that causes the harmful effects and renal damage⁹.

Adding to that asymptomatic bacteriuria (positive urine cultures, with or without pyuria, without accompanying genitourinary symptoms attributable to infection) is regarded as harmless and is not an indication for treatment^(8,14).

Available data about prevalence of pyuria in general community is scare, but in our study it was found in (7.7%) of the randomly selected control group (465 patients) who were seeking medical advice for conditions not related to genitourinary complaints.

Culture: Despite availability of molecular diagnostic approaches for diagnosis of many infections, UTI are still generally diagnosed, as they have been for decades, by urine culture results⁽⁷⁻⁹⁾. However, urine culture may not be necessary as part of the evaluation of outpatients with uncomplicated UTIs^(13,14).

Positive urine culture results were obtained from 38 (8.2%) patient in the urticaria group, while such results were found in 11 (2.4%) urine samples from the control group. When these figures were statistically tested, the association between urticaria and positive urine culture was found to be a highly significant association, (with a p value < 0.001).

Comparison of these results with data obtained from other studies is impeded by variable differences between study designs¹⁵.

Prevalence of community-associated UTI was reported to be 0.7%, However frequency of UTIs vary according to geographical setting and location, and providing exact figures is challenging^(6,16). Positive culture results were found in 11 (2.4%) urine samples from the control group, those were assumed to be asymptomatic since they were attending clinics for complaints not primarily related to genitourinary complaints. However, when those with positive culture results were carefully questioned about symptoms related to UTIs, positive and negative replies were obtained and thus constituting a hybrid between UTIs and asymptomatic bacteriuria.

Pyuria has multiple causes¹⁷, and we concentrate in current study on UTIs but others should be considered in cases where culture is Negative

The exact mechanism of how infectious agents cause urticaria is not known^(10,11). It is accepted that hives are caused by “friendly fire” from the human body’s own defenses rather than caused directly by the infectious agents. It has been postulated that these agents trigger release of histamine and leukotrienes from the mast cells and basophils by IgE antigen complex; or through anaphylotoxin C3a, C4a generated through activation of complement system or through the kinins, e.g., bradykinin^(11,18).

Conclusion

Though establishing a causal relationship through experimental study is difficult, this study showed a highly significant association between bacterial UTI and spontaneous urticaria.

Further prospective studies to elucidate effect of eradicating UTIs on course of urticaria is advisable.

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Conflict of Interest: None to declare.

Ethical Clearance: All experimental protocols were approved under the College of Medicine, University of Thi-Qar, Iraq and all experiments were carried out in accordance with approved guidelines.

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