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Etiological causes in patients with acute urticaria and angioedema: A cross-sectional study

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Abstract
Background: Acute urticaria and angioedema are emergency dermatological conditions associated with various etiologic factors.
Objective: To determine the etiological causes in patients with acute urticaria and angioedema, and to investigate whether more than one etiological cause was present, along with the patients' laboratory values.
Methods: The study was conducted in a tertiary hospital with one center. Etiological causes and laboratory parameters in 284 patients diagnosed with acute urticaria and angioedema were retrospectively studied.
Results: A total of 284 patients were included in the study. The mean age of the patients was 42.7 ± 15.6 years, where 163 (57.4%) were women and 121 (42.6%) were men. Acute urticaria and angioedema occurred together in 149 (52.5%) patients. At least one precipitating factor among the predisposing risk factors was present in 220 (77.5%) patients, and more than one precipitating factor was found in 51 (18%) patients. Medication use was found in 157 (55.3%) patients and infection in 54 (19%). The development of urticaria after food consumption was noted in nine (3.2%) individuals. A history of infection and medication intake was present in 50 (17.6%) patients. A joint history of food consumption and medication intake was present in only one patient. Elevated C-reactive protein level was found in 178 (62.7%) patients and elevated anti-streptolysin O titer in 41 (14.4%) patients. Vitamin B12 deficiency was found in 116 (40.8%) patients and vitamin D deficiency in 254 (89.4%).
Conclusion: Acute urticaria and angioedema may occur as a result of multiple etiological factors, in which different triggers may be present simultaneously.

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Introduction

Acute urticaria is a dermatological condition that may be accompanied by angioedema and is characterized by pruritic and edematous papules or plaques. The lesions usually disappear in less than 24 h. Acute urticaria lasts less than 6 weeks. Angioedema is a life-threatening condition characterized by transient edema of the skin and/or mucous membranes that is not sharply circumscribed and may involve deeper tissues and usually resolves within 72 h. Urticaria is often a mast cell-mediated condition. It can occur by immunologic or nonimmunologic mechanisms. Angioedema may occur with a mechanism similar to urticaria, or it may occur after vascular permeability induced by increased bradykinin with irregular activation of the Kinin pathway.[1] In some studies, the incidence of acute urticaria was reported to be 18.7%.[2] Factors such as different eating habits and environments, and socioeconomic and occupational statuses may lead to different allergens. Therefore, the frequency and variety of etiological factors may vary in different geographic regions.

Urticaria is a disease that has a negative impact on patients' quality of life. It also represents a major economic burden for patients.[3]

Medications, infections, and food have been shown to be the most common etiological causes of acute urticaria. The frequency and variety of infections can vary based on patient population and geographic region.[4] The most commonly implicated medications are angiotensin-converting enzyme (ACE) inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs).[5]

The first stage of diagnosis of acute urticaria consists of a detailed history and physical examination. Because the disease may be self-limiting and attacks are of short duration, some studies do not recommend a detailed etiologic examination.[3] This study investigated the etiological causes in patients with acute urticaria and angioedema and the laboratory findings of these patients.

Materials and Methods

Study design and patients

This study was designed as a cross-sectional study and was conducted in a single center in Erzurum, Turkey. The study was conducted in accordance with the tenets of the Declaration of Helsinki after receiving approval from the local ethics committee (Decision number: 30.12.2021/8).

The sample population was all patients who presented to the Department of Dermatology, Faculty of Medicine, Ataturk University, between December 2017 and December 2021. The total number of patients during this period was set at 7495. Hospital records were retrospectively scanned using International Classification of Diseases (ICD-10) codes, and patients diagnosed with urticaria and angioedema with codes L50, L50.0, and T78.3 were included. Patients below 18 years or above 80 years or whose symptoms lasted longer than 6 weeks were excluded. Patients with angioedema who had a family history of the condition were also excluded. The total number of eligible patients was 284 (3.8%).

None of the patients had symptoms or signs suggestive of anaphylaxis. Patients' sociodemographic characteristics and history of medication use, food consumption, concomitant infection, and other systemic diseases were recorded as potential precipitating factors in the epicrisis records. Laboratory values from our hospital were used as the reference values of the test results. Accordingly, white blood cell (WBC) 4000–11,000/μL, hemoglobin >12 g/dL, anti-streptolysin O (ASO) < 200 IU/mL, C-reactive protein (CRP) < 5 mg/L, glucose 60–100 mg/dL, Vitamin B12 200–1000 pg/mL, Vitamin D 25–80 ng/mL, folate 3–20 ng/mL, ferritin 20–300 ng/mL, thyroid-stimulating hormone (TSH) 0.5–4 mIU/mL, free T4 (FT4) 0.58–1.38 pmol/L, total Immunglobulin E (IgE) 26–100 IU/mL, iron 70–180 mg/dL, unsaturated iron binding capacity (UIBC) 155–300 mg/dL, alanine aminotransferase (ALT), aspartate aminotransferase (AST) < 50 U/L, and gamma-glutamyl transferase (GGT) < 60 U/L were considered normal reference values.

Statistical analysis

Study data were analyzed using SPSS version 23.0 software (IBM, NY, USA). Categorical data were expressed as frequency and percentage, and numerical data were expressed as mean + standard deviation. Normality of distribution was tested using the Kolmogorov–Smirnov test. Student's t-test was applied when comparing two independent data in case of normal distribution, while Mann–Whitney U test was used in case of non-normal distribution. The chi-square test was used in the analysis of categorical data. Univariate regression test was performed to determine the risk association of the variables. $P < 0.05$ was considered statistically significant.

Results

Patients' demographic characteristics

A total of 284 patients, comprising 57.4% (n = 163) women and 42.6% (n = 121) men were included in the study. The mean age of the patients was 42.7 ± 15.6 years, and the mean duration of urticaria symptoms was 4.0 ± 5.5 days. Angioedema was present in 52.5% (n = 149) of the patients with urticaria (Table 1).

Accompanying chronic systemic diseases

The most common chronic disease among the patients was thyroid disease (6.7%, n = 19), while 87% (n = 247) had no chronic diseases. Hyperthyroidism was present in 2.1% (n = 6) of the patients with thyroid disease, hypothyroidism in (0.7%, n = 2), and other thyroid diseases in (3.9%, n = 11). Hypertension was present in 1.8% (n = 5) of the patients, diabetes in 3.2% (n = 9), and malignancy (hematological cancer) in only about 0.4% (n = 1) (Table 1).

Table 1 Patients' demographic characteristics and factors predisposing to urticarial.

			N	%	P*
Sex	With angioedema	Male	71	47.7	0.071
		Female	78	52.3	
	Without angioedema	Male	50	37	
		Female	85	63	
	Total		284	100	
Age (years, mean, standard deviation)	With angioedema		41.7	15.0	0.344
	Without angioedema		43.8	16.2	
	Total		42.7	15.6	
Duration of urticaria symptoms (days, mean, standard deviation)			4.0	5.5	
Presence of angioedema			149	52.5	
Accompanying chronic disease	Thyroid disease	Total	19	6.7	
		Hyperthyroidism	6	2.1	
		Hypothyroidism	2	0.7	
		Other diseases	11	3.9	
	Diabetes mellitus		9	3.2	
	Hypertension		5	1.8	
	Malignancy		1	0.4	
	Other diseases		3	1.1	
Predisposing factors	History of medication use		157	55.3	
	Infection	Total	54	19.0	
		URTI*	44	15.5	
		Dental infection	6	2.1	
		Urinary infection	3	1.1	
		LRTI†	1	0.4	
	Food history	Total	9	3.2	
		Packaged ready-to-eat food	5	1.8	
		Peanut	1	0.4	
		Chocolate	1	0.4	
		Herbal tea	1	0.4	
		Fruit	1	0.4	
	Medication use + Infection		50	17.6	
	Medication + Food history		1	00.4	
	Infection + Food history		0	0	
	Infection + Medication + Food history		0	0	
	Total		271	95.4	
	Unknown		13	40.6	

LRTI: Lower respiratory tract infection; URTI: Upper respiratory tract infection. *Mann-Whitney U test.

Causes of acute urticaria in our patients

The distribution of the predisposing risk factors that have been evaluated as causing the development of urticaria is shown in Figure 1.

The most common factor predisposing to the development of urticaria was medication use, which was observed in 55.3% (n = 157) of the patients. This was usually a single medication (43.7%, n = 124), and less frequently two (9.9%, n = 28) or three (1.8%, n = 5) medications. The most commonly used medication type was NSAIDs (18.3%, n = 52), followed by antibiotics (16.9%, n = 48), NSAIDs and antibiotics combined (6%, n = 17), and paracetamol (4.6%, n = 13) (Table 2).

The most commonly used NSAIDs among 25% (n = 71) of the patients who used NSAIDs, either alone or with other medications, were propionic acid derivatives (14.8%, n = 42), followed by acetic acid derivatives (3.9%, n = 11), acetylsalicylic acid (3.5%, n = 10), and phenyramidol (2.8%, n = 8). The most frequently used antibiotics were from the penicillin group (15.5%, n = 44) and the cephalosporin group (6%, n = 17), followed by fluoroquinolones (2.5%, n = 7), macrolides (1.1%, n = 3), and tetracyclines (0.4%, n = 1). Two patients were taking angiotensin receptor blockers, and ACE inhibitors, beta blockers, and calcium channel blockers were used by one patient each (Table 2).

The second most common predisposing cause of urticaria was infection, which was found in 19% (n = 54) of the patients. Upper respiratory tract infection (URTI) was present in 15.5% (n = 44) of these patients, dental infection in 2.1% (n = 6), known chronic urinary tract infection (UTI)

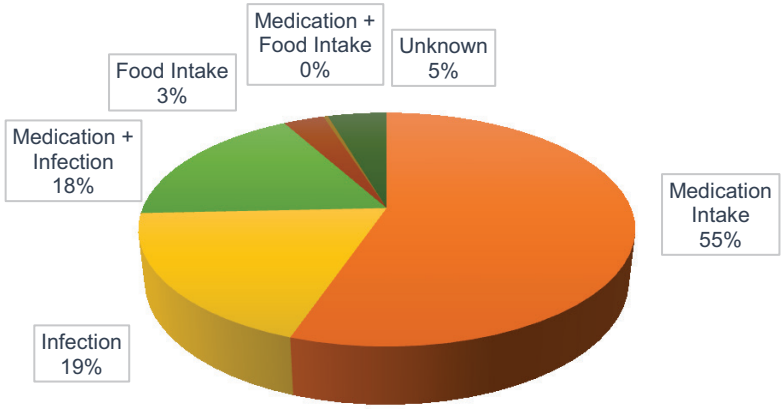

Figure 1 Urticaria predisposing factors.

Table 2 Medications identified as causing urticarial.

		N	%
Number of medications	None	127	44.7
	One	124	43.7
	Two	28	9.9
	Three	5	1.8
Medication groups	NSAID	52	18.3
	Antibiotics	48	16.9
	Antibiotic + NSAID	17	6.0
	Paracetamol	13	4.6
	Paracetamol + Antibiotic	7	2.5
	Contrast material	5	1.8
	Antihypertensive	3	1.1
	Mucolytic	2	0.7
	NSAID + Antihypertensive	2	0.7
	Antiepileptic	1	0.4
	Laxatives	1	0.4
	Spasmolytic	1	0.4
	Proton pump inhibitor	1	0.4
	Others	4	1.4
NSAID group	Propionic acid derivative	42	14.8
	Acetic acid derivative	11	3.9
	Acetyl salicylic acid	10	3.5
	Phenyramidol group	8	2.8
Antibiotic group	Penicillin group	44	15.5
	Cephalosporin group	17	6.0
	Fluoroquinolone group	7	2.5
	Macrolide group	3	1.1
	Tetracycline group	1	0.4
Total		**284**	**100.0**

NSAID: Non-steroid anti-inflammatory drug.

in 1.1% (n = 3), and lower respiratory tract infection (LRTI) in 0.4% (n = 1). Concurrent medication use and history of infection were identified in 17.6% (n = 50) of the patients. Concomitant medication and food consumption were found in only one patient (Table 1).

Urticaria developed in 3.2% (n = 9) of the patients after food consumption. This occurred in five of the nine patients after consumption of packaged ready-to-eat foods, and in one patient each after consumption of peanuts, chocolates, herbal tea, and fruits (Table 1).

Laboratory findings

Our test results were classified as low, normal, or high based on our hospital's laboratory reference values, and the results are shown in Table 3.

An elevation of leukocytes was observed in 52.8% (n = 150) of the patients. Elevated CRP level was seen in 62.7% (n = 178) of the patients and elevated ASO in 14.4% (n = 41). Low hemoglobin levels were noted in 12% (n = 34) of the patients, low ferritin levels in 20.8% (n = 59), and low iron levels in 59.5% (n = 169). Vitamin B12 deficiency was found in 40.8% (n = 116) of the patients, folic acid deficiency in 4.2% (n = 12), and Vitamin D deficiency in 89.4% (n = 254). Total IgE levels were high in 20.8% (n = 59) of the patients. A history of urinary infection, a known factor predisposing to urticaria, was present in only 1.1% (n = 3); UTI was detected in 39.1% (n = 111) of the patients based on complete urinalysis (Table 3).

The associations and comparison of factors predisposing to urticaria with medical history and laboratory test result categories are shown in Table 4.

Significant increase in blood cell count and Vitamin B12 deficiency were found in patients with concomitant angioedema (P = 0.030, P = 0.005, respectively). Significant UTIs were also noted in patients taking medications and had an infection (P = 0.016).

In univariate regression analysis, all categorical and numerical variables were found to be statistically insignificant, hence multivariate regression analysis was not performed.

Discussion

Main findings

In this study, urticaria was found to be accompanied by angioedema in 52.5% of the patients, and the most common chronic condition was thyroid disease. However, the strongest predisposing factor for angioedema was medication use (55.3%). The second most important predisposing factor was infection at a rate of 19%, with both medication

Table 3 Classification of laboratory test results according to reference values.

		N	%
WBC levels	Low	2	0.7
	Normal	132	46.5
	High	150	52.8
Hemoglobin levels	Low	34	12.0
	Normal	250	88.0
Iron levels	Low	169	59.5
	Normal	115	40.5
UIBC levels	Low	1	0.4
	Normal	230	81.0
	High	53	18.7
Ferritin levels	Low	59	20.8
	Normal	218	76.8
	High	7	2.5
CRP levels	Normal	106	37.3
	High	178	62.7
ASO levels	Normal	243	85.6
	High	41	14.4
Glucose levels	Low	4	1.4
	Normal	135	47.5
	High	145	51.1
HbA1c levels	Normal	263	92.6
	High	21	7.4
Vitamin B12 levels	Low	116	40.8
	Normal	163	57.4
	High	5	1.8
Vitamin D levels	Low	254	89.4
	Normal	28	9.9
	High	2	0.7
Folate levels	Low	12	4.2
	Normal	269	94.7
	High	3	1.1
Total IgE levels	Low	104	36.6
	Normal	121	42.6
	High	59	20.8
ALT levels	Normal	278	97.9
	High	6	2.1
AST levels	Normal	279	98.2
	High	5	1.8
GGT levels	Normal	274	96.5
	High	10	3.5
TSH levels	Low	77	27.1
	Normal	192	67.6
	High	15	5.3
FT4 levels	Low	10	3.5
	Normal	267	94.0
	High	7	2.5
Thyroid Autoantibody	Negative	273	96.1
	TSH receptor Antibody positive	6	2.1
	Microsomal Antibody positive	5	1.8
Urinary infection	Negative	173	60.9
	Positive	111	39.1
Parasite test in feces	Negative	283	99.6
	Positive	1	0.4
Helicobacter pylori	Negative	280	98.6
	Positive	4	1.4
Hepatitis B test	Negative	278	97.9
	Positive	6	2.1
Total		284	100.0

ALT: Alanine transaminase; ASO: Anti-streptolysin O; AST: Aspartate transaminase; CRP: C-reactive protein; FT4: Free T4; GGT: Gamma-glutamyl transferase; HbA1c: Glycosylated hemoglobin; IgE: Immunglobulin E; TSH: Thyroid-stimulating hormone; UIBC: Unsaturated iron-binding capacity; WBC: White blood cell.

use and infection, observed in 17.6% of patients. The most commonly used medications were NSAIDs and antibiotics. When the patients' laboratory test results were examined, it was found that WBC and vitamin B12 levels were statistically different among patients with angioedema.

Methodology

Acute urticaria is a condition with a prevalence of 10–25% that may occur either alone or together with angioedema.[3] Although it is common, there are very few studies on its etiology. The etiological causes of acute urticaria have been studied mainly in pediatric patients. The aim of the present study was to investigate the etiological causes and prevalence in adult patients with acute urticaria and/or angioedema and to determine the laboratory parameters of these patients and how many of them have more than one etiological cause.

Comparison with other studies

Studies shows that 15–23% of the population is at risk of experiencing acute urticaria and/or angioedema attacks at some point in their lives.[6] Köse et al.[7] reported that 71.8% of patients with urticaria were women, with an average age of 28 years. In another study, Losappio et al.[8] reported that 42.9% of their patients with acute urticaria were women, with a mean age of 35. In the present study, women accounted for 57.4% (n = 163) of the patients, and men accounted for 42.6% (n = 121). The mean age of the patients was 42.7 ± 15.6 years. In agreement with the previous literature, female gender was more prevalent. However, the reason for the higher prevalence of acute urticaria in females is not yet fully understood.

Reportedly, urticaria and angioedema occur together in 40% of the cases, urticaria alone in 40%, and angioedema alone without urticaria in 11–20%.[9] In this study, angioedema was present in 52.5% (n = 149) of the patients with urticaria.

The symptoms of acute urticaria usually last less than 6 weeks.[10] The mean duration of urticaria symptoms in this study was 4.0 ± 5.5 days.

Table 4 Comparison of factors predisposing to urticaria and patient histories with laboratory test result categories.

	Angioedema	Infection	Food history	Medication intake	Medication intake + Infection	Medication intake + Food history
WBC levels*	0.030**	0.801	0.060	0.030**	0.375	0.527
Hemoglobin levels*	0.501	0.987	0.606	0.163	0.805	1
ASO levels*	0.615	0.463	0.366	0.650	0.312	1
CRP levels*	0.405	0.025**	0.083	0.256	0.068	0.373
Glucose levels*	0.060	0.361	0.462	0.003**	0.818	0.474
HbA1c levels*	0.814	0.775	0.504	0.613	1	1
Vitamin B12 levels*	0.005**	0.750	0.259	0.499	0.320	0.407
Vitamin D levels*	0.403	0.970	0.931	0.970	0.518	0.894
Folate levels*	0.520	0.072	0.609	0.689	0.076	0.947
Ferritin levels*	0.579	0.706	0.571	0.569	0.812	0.767
TSH levels*	0.097	0.821	0.761	0.572	0.612	0.675
FT4 levels*	0.783	0.332	0.568	0.619	0.168	0.940
Total IgE levels*	0.304	0.396	0.220	0.823	0.325	0.365
Iron levels*	0.420	0.203	0.165	0.118	0.068	0.405
UIBC levels*	0.411	0.966	0.145	0.407	0.815	0.810
ALT levels*	0.105	1	1	1	1	1
AST levels*	0.671	1	1	0.385	1	1
GGT levels*	0.753	1	1	0.026**	0.690	1
Thyroid autoantibody levels*	0.728	0.597	0.029**	0.945	0.307	0.961
Urinary infection*	0.078	0.012**	0.740	0.286	0.016**	1
Parasite in stool*	1	1	1	1	1	1
*Helicobacter pylori**	0.349	0.572	0.121	0.328	0.541	1
Hepatitis B*	0.686	0.320	1	0.230	0.285	1

*Categorized as low, normal or high according to reference values. The Chi-square test was applied. **P < 0.05 was regarded as statistically significant.
ALT: Alanine transaminase; ASO: Anti-streptolysin O; AST: Aspartate transaminase; CRP: C-reactive protein; FT4: Free T4; GGT: Gamma-glutamyl transferase; HbA1c: Glycosylated hemoglobin; IgE: Immunglobulin E; TSH: Thyroid-stimulating hormone; UIBC: Unsaturated iron-binding capacity; WBC: White blood cell.

Etiological causes cannot be identified in 30–50% of patients with acute urticaria.[11] No etiological cause could be identified in 4.6% (n = 13) of the 284 patients in the present study. A good history and physical examination are essential to determine the likely precipitating factor in patients diagnosed with acute urticaria. Studies have reported that the etiology can be determined in 72–86% of the cases of acute urticaria with the help of a detailed history.[4]

Some studies have pointed to systemic diseases associated with urticaria, especially in patients with chronic urticaria. However, in their study of patients with acute urticaria, Karadağ et al.[12] reported concomitant systemic disease in 14% of the cases.

Similarly, in the present study, chronic disease was found in 13.2% (n = 37) of the patients, with thyroid disease being the most common (6.7%, n = 19).

These data suggest that systemic diseases do not occupy an important place in the etiology of acute urticaria.

The most common precipitating factors in patients with acute urticaria are infections, medications, past history of food, and insect bites.[4]

Several studies have described infections as the most common factor in the etiology of acute urticaria. About 10–27% of medication-related urticaria cases have been reported.[11] In contrast to the previous literature, in the present study, medication use was identified as the most common etiological factor in 55.3% (n = 157) of the patients.

Some patients in this study were taking only one medication, whereas others were taking multiple medications. A single medication was taken by 43.7% (n = 124) of the patients, 9.9% (n = 28) were on two medications, and 1.8% (n = 5) were on three medications. When examining medication use as a predisposing factor in patients, it should be kept in mind that more than one medication may be involved in combination. Both prescription medications and herbal and alternative medications should be investigated to rule out the predisposing factor.

Drugs can lead to manifestation of acute urticaria via both immunological and nonimmunological mechanisms.[13] The drug groups that most commonly involved in drug-induced acute urticaria are antibiotics and NSAIDs.[14]

NSAIDs and ACE inhibitors are the most common causes of drug-induced angioedema. About 76% of NSAID-related hypersensitivity reactions are nonimmunological in nature, and 24% are immunologic. Inhibition of the enzyme cyclooxygenase-1 (COX-1) may be involved in the

nonimmunological mechanism.[15] In the present study, NSAIDs were taken either alone or in combination with other drug groups by 71 patients and were the most common causes for cases of drug-induced acute urticaria. We hypothesize that this is because NSAIDs are the most commonly prescribed drug group in Turkey and worldwide.[16]

Analysis of the NSAID groups revealed that propionic acid derivatives were the most commonly used (n = 42), followed by acetic acid derivatives (n = 11), acetyl salicylic acid (n = 10), and phenyramidol (n = 8). Acute urticaria was also noted in 13 patients after paracetamol use.

The second most frequently identified drug group in this study was antibiotics. The number of patients who had taken antibiotics alone (n = 48) or in combination with other medications (n = 72) was determined. The most commonly used antibiotics were the penicillin (n = 44) and cephalosporin (n = 17) groups, followed by the fluoroquinolone (n = 7), macrolide (n = 3), and tetracycline (n = 1) groups.

Antibiotics of the beta-lactam group are the most commonly used antibiotics worldwide and the most common causes of drug-induced allergic reactions.[17,18] Antibiotic-induced acute urticaria can be IgE-dependent or independent.[19]

In the present study, antibiotic-induced urticaria was most commonly seen in association with antibiotics of the beta-lactam group, such as penicillin and cephalosporin. Some patients were on antibiotics alone, whereas others were on concomitant NSAIDs and antibiotics (n = 17) or acetaminophen and antibiotics (n = 7). It is not possible to determine whether the manifestations of acute urticaria in these patients were triggered in association with NSAIDs or antibiotics.

Infections have been described as the most common etiological cause of acute urticaria.[1,4] Although the pathogenesis of infection-related urticaria has not been fully elucidated, it may be due to the action of toxins of microorganisms or complement activation mediated by immune complexes in the bloodstream.[20]

A review of five studies reported that viral URTIs were present in 50% of patients with urticaria.[21] In the present study, infections were found to be the second most common predisposing factor for the development of urticaria. Because laboratory tests for viral infections were not performed in this study, we believe that our results probably do not accurately reflect the rate of infection.

In this study, 54 (19%) patients were found to have an infection, including URTI (n = 44), dental infection (n = 6), known urinary infection (n = 3), and LRTI (n = 1).

Although 44 of the 54 patients with an infection, in this study, had a history of URTI, it was not possible to determine whether this was related to viral or bacterial infections because of the retrospective nature of the study. A previous study reported significantly higher ASO titers in patients with refractory urticaria compared with control subjects.[22] ASO was also high in the present study, in 14.4% of the patients.

Acute urticaria may be associated with UTIs. In a study of 105 patients with acute urticaria, 33 (22.5%) patients were found to have an infection, of which 8 (7%) were associated with a UTI.[12] In the present study, based on patients' self-reports, a known UTI was present in only 1.1% (n = 3) of the cases. UTI was detected in 39.1% (n = 111) of the patients based on complete urinalysis. We think that this high rate could be due to contamination. However, the fact that urine culture was not performed limited our ability to identify UTIs.

There were no studies in the literature that showed an association between Vitamin B12 deficiency and acute urticaria. The relationship between Vitamin B12 levels and the pathogenesis of urticaria is not fully understood, although the micronutrient is thought to regulate the release of cytokines after mast cell degranulation through its immunomodulatory properties.[23] In the present study, Vitamin B12 levels were below normal laboratory parameters in 40.8% (n = 116) of the cases. We think that this rather high number is due to the low socioeconomic status and dietary habits of our region.

The prevalence of angioedema in this study was significantly higher in patients with Vitamin B12 deficiency (P = 0.005). We believe that further, more extensive studies are needed to determine the relationship between Vitamin B12 deficiency and angioedema, the possible pathogenesis, and the impact of Vitamin B12 supplementation on prognosis.

In this study, hemoglobin levels were low in 12% (n = 34) of the patients, iron levels in 59.5% (n = 169), and ferritin levels in 20.8% (n = 59).

A search of the literature did not reveal any previous studies on the association between iron deficiency and acute urticaria. We believe that prospective studies are needed to clarify this possible association.

Vitamin D receptors are located on the surface of immune cells and regulate both innate and adaptive immune response. Active 1,25-(OH) Vitamin D makes antigen-presenting cells more tolerant and immature. It may also reduce immunoglobulin synthesis by decreasing B cell proliferation.[24]

One study showed a decrease in in-vitro IgE production after Vitamin D administration.[25] A study on pediatric patients with acute urticaria also found significantly lower Vitamin D levels compared to the control group.[26] In the present study, Vitamin D levels were below the reference laboratory values in 254 (89.4%) of the patients.

Similar to other parts of the world, Vitamin D deficiency is widespread in Turkey. We attribute this to the geographic conditions and sun exposure rates of our region.[27] Because of its immunomodulatory properties, we believe that prospective studies are needed to investigate whether Vitamin D supplementation may be beneficial in patients with acute urticaria.

Strong points

The strengths of our study include the following. Firstly, this is one of the unique studies on angioedema and urticarial risk factors. Secondly, the study was conducted in a tertiary hospital serving 4.5 million inhabitants in 12 provinces in Eastern Turkey. This provided an opportunity to observe and collect important regional data in this area, which made it possible to draw conclusions about urticaria risk factors in the region. Thirdly, in addition to predisposing risk factors for angioedema, their subgroups and combined risk factors were identified. Finally, the study included high number of patients, as it covered a period of 4 years.

Potential confounders and limitations

The main limitations of this study are its retrospective nature, and because patients were not screened for viral infections, we do not believe that our results accurately reflect the incidence of infections. Secondly, although the study was conducted in a tertiary hospital serving surrounding provinces, the fact that the study was conducted in a single center is a limitation. Thirdly, the fact that urine cultures were not performed is a limitation in determining the frequency of infection. The lack of allergy testing was also limitation. Also, the patients' laboratory data were not compared with those of the control group, which was another limitation.

Conclusion

In conclusion, it is useful to consider medications, infectious foci, and nutritional history in the etiology of acute urticaria. Consistent with previous literature, in this study, medications and infections were most frequently detected in the etiology of acute urticaria. Because urticaria is generally a spontaneously resolving condition, comprehensive investigation for precipitating factors is not recommended unless supported by history and physical examination. We believe that more than one etiological causes may converge in triggering of acute urticaria, that many laboratory parameters may be abnormal, and that tests should be performed based on the history and physical examination findings of patients with acute urticaria.

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