Acta Dermatovenerol Croat 2015;23(1):36-42 CLINICAL ARTICLE

Evaluation of Etiological Factors in Patients with Chronic Urticaria

Emine Colgecen[1], Kemal Ozyurt[2], Ali Irfan Gul[3], Serap Utas[4]

[1]Department of Dermatology, Faculty of Medicine, Bozok University, Yozgat, Turkey;
[2]Department of Dermatology, Kayseri Training and Research Hospital, Kayseri, Turkey;
[3]Department of Psychiatry, Faculty of Medicine, Bozok University, Yozgat, Turkey;
[4]Department of Dermatology, Acibadem Fulya Hospital, Istanbul, Turkey

Corresponding author:
Emine Colgecen, MD
Bozok University Medical Faculty
Department of Dermatology
TR-66000 Yozgat
Turkey
drecolgecen@hotmail.com

Received: May 9, 2014
Accepted: December 15, 2015

ABSTRACT In the last few decades, increasing understanding of the pathomechanisms involved in chronic urticaria has highlighted the heterogeneity of different subtypes, and chronic urticaria is now classified as chronic spontaneous urticaria and inducible urticaria. Although many factors are thought to be involved in chronic urticaria, the etiology is yet to be clarified. The purpose of this study was to investigate etiological factors in patients with chronic urticaria.
Five hundred patients with chronic urticaria, 351 women and 149 men, were studied for etiological factors. The autologous serum skin test was performed on 197 patients. Provocation testing for physical urticaria was performed on 354 patients. Patients with acute urticaria were excluded from the study. We determined at least one focus of infection that might be involved in the etiology of the disease in 18.8% of cases. Patients with infections were treated, and symptoms resolved after treatment in six cases (5.3%). Autologous serum skin tests were positive in 125 patients (63.5%). Provocation tests for physical urticaria were positive in 131 (37%) patients with urticaria. We suggest that physical stimuli and autoantibodies play an important role in the etiopathogenesis of urticaria.

KEY WORDS: urticaria, etiopathogenesis, physical urticaria, autologous serum skin test

INTRODUCTION

Chronic urticaria has been divided into two subgroups by the European Academy of Allergy and Clinical Immunology (EAACI), Global Allergy and Asthma European Network (GA²LEN), European Dermatology Forum (EDF), and World Allergy Organization (WAO): chronic spontaneous urticaria and inducible urticaria (1,2).

Any form of urticaria recurring two times a week for six weeks are classified as chronic urticaria (3,4). This form of the disease usually appears in adults between 20 and 45 years of age. Women are affected twice as frequently as men (5,6).

Chronic urticaria accounts for 5-20% of all urticaria cases, and the cause is unknown in 70-90% (7,8). According to recent evidence, some 30% of chronic urticaria cases have been associated with autoimmunity, and approximately 20-50% of chronic urticaria cases are caused by physical agents. Most studies of chronic urticaria have shown that when the etiological agent is not identified at history and examination, it is almost impossible to identify it through other investigations (1,7). Our aim was therefore to determine etiological factors in patients presenting with chronic urticaria to our dermatology outpatient clinic.

STUDY PARTICIPANTS AND METHODS

The study included 500 patients presenting with chronic urticaria to Dermatology Outpatient Clinic of the Yozgat Bozoh University Medical Faculty and

Kajseri Training and Research Hospital between October 2010 and April 2014. Demographic features, types and duration of urticaria, medications used, accompanying diseases, and findings from physical examinations and laboratory investigations were recorded on patient follow-up forms. Patients with acute urticaria were not included in the study.

At first presentation, patients were asked to complete a brief questionnaire about possible causes of urticaria. They were then interviewed in detail about the items they marked. Patients were then examined. Complete blood count, erythrocyte-sedimentation rate, routine biochemical investigations, hepatitis markers, thyroid function tests, thyroid autoantibodies (antimicrosomal and antithyroglobulin), complete urine analysis, and examination of parasites in faeces were requested. Complements and C1 esterase inhibitor levels in cases of urticaria accompanying angioedema and immunoglobulin E (IgE) levels in cases of urticaria with a history of atopia were determined. The prick test was performed when necessary. Based on the results obtained, further investigations were performed and consultations with relevant medical disciplines were requested.

In order to identify and exclude physical urticarias (PUs) and autoimmune urticaria, antihistamine treatment was withheld for at least three days in patients unlikely to be affected by this discontinuation, and appropriate provocation tests and autologous serum skin tests were carried out. No patients were using antihistaminics with an effect lasting for more than 24 hours.

For diagnosis of symptomatic dermographism, trauma to the back or the forearm was induced with a blunt-tipped device. One or three minutes later, trauma-related urticaria development was evaluated. To evaluate late pressure urticaria, pressure (3-4 kg) was applied to the forearm for five minutes. The resulting erythematous plaques were examined after 30 minutes and after eight hours. In order to evaluate acquired cold urticaria, an ice cube was placed on the inner side of the forearm for 5-15 minutes, and the resulting urticaria was evaluated 5-15 minutes later. Anti-nuclear antibody (ANA), cryoglobulin, cold agglutinins, and cryofibrinogen were investigated in all patients with a history of acquired cold urticaria. In order to evaluate hot urticaria, a plastic tube containing hot water at 40-50˚C was placed on the inner side of the forearm for five minutes, and the resulting lesion was evaluated for urticaria development 5-10 minutes later. In order to evaluate solar urticaria, body parts were examined 1-3 minutes after exposure to artificial ultraviolet rays. For cholinergic urticaria evaluation, patients were asked to walk at a constant speed for 10-15 minutes until they perspired. Development of urticaria was then investigated.

Autologous serum skin test (ASST) was administered to 197 patients. An intradermal injection of 0.05 ml serum derived from venous blood was performed to the inner side of the forearm. When erythema and edema appearing 30 minutes after the injection had a diameter at least 15 mm greater than that caused by injection of the control solution (NaCl), the test result was considered positive.

RESULTS

Of the 369 patients with chronic urticaria in this study, 259 were women and 110 men. The patients were aged 5-74 years, with a mean age of 37.15-12.71 years. Duration of the disease ranged from six weeks to 33 years, with a mean of 3.87±5.13 years. Angioedema accompanied the disease in 228 cases (61.8%).

Two hundred and fifteen patients (58.1%) had leukocytosis. Of these, six (2.8%) had gastritis, five (1.4%) tooth decay, five (1.4%) urinary tract infection, three (0.8%) pelvic inflammatory disease, and three (0.8%) cholelithiasis. Out the 19 patients determined to have eosinophilia (5.1%), five (15.8%) had a history of atopia, two (10.5%) had increased IgE, seven (36.8%) had *Blastocystis hominis* in faeces, and two (10.5%) had *Taenia saginata*. Fifteen patients (4.1%), 10 (2.7%) women and five (1.4%) men, had anaemia. Of the 27 patients determined to have increased sedimentation rates (7.3%), nine (33.3%) exhibited leukocytes and bacteria at urine analyses, four (14.8%) had anaemia, three (11.1%) had tooth decay, three (11.1%) sinus-

Table 1. Responses of infections detected in patients with chronic urticaria to treatment

Urticaria subsiding with treatment for infection	Urinary infection	Sinusitis	Parasitosis	Hepatitis B and C	URTI	Vaginitis and PID
Yes	0	0	4 (%1.1%)	0	0	2 (0.5%)
No	26 (7.0%)	29 (7.8%)	68 (18.4%)	20 (5.4%)	2 (0.5%)	9 (2.5%)
Total	26 (7.0%)	29 (7.8%)	72 (19.5%)	20 (5.4%)	2 (0.5%)	11 (3.0%)

URTI: upper respiratory tract infection; PID: pelvic inflammatory disease

Table 2. Distribution of autologuous serum skin test (ASST) positivity by genders

	ASST		
Gender	Negative	Positive	Total
Female	47 (37.3%)	79 (62.7%)	126 (100.0%)
Male	25 (35.2%)	46 (64.8%)	71 (100.0%)
P>0.05	72 (36.5%)	125 (63.5%)	197 (100.0%)

itis, three (11.1%) hepatitis B infection, three (11.1%) internal malignity (thyroid lymphoma, breast carcinoma), and two (7.4%) hepatitis C infection.

Leukocytes and bacteria were observed at urine analysis in 84 patients (22.7%). *Escherichia coli* was isolated in the urine culture of four patients. Urticaria did not resolve in the patients receiving treatment for urinary tract infection. *B. hominis* was determined in 103 patients (27.8%) at laboratory investigations for parasites in faeces, and those patients with symptoms for the parasites were treated. In addition, four patients (1.1%) had *Giardia intestinalis*, six (1.6%) had *Entamoeba histolytica*, two (0.5%) had *Entamoeba coli*, and two (0.5%) had *T. saginata*. Urticaria subsided in two patients with giardiasis and two patients with amoeba after treatment for these parasites. Investigations for other sources of infection revealed sinusitis in 29 patients (7.8%), hepatitis B positivity in 14 (3.8%), hepatitis C positivity in six (1.6%), sore throat with hemolytic β streptococcus in two (0.5%), vaginitis in 10 female patients (2.7%), and pelvic inflammatory disease in one female patient (0.3%). Treatment for infection led to an improvement in urticaria in only one female patient with vaginitis (Table 1).

Of the 39 patients with a history of atopia (10.5%), 25 had IgE levels exceeding 100 mg/dl. Thirty-five patients were administered the prick test, and allergy to one or more substances was determined in 16 patients (4.3%). The most frequent allergens were *Dermatophagoides farinae, Dermatophagoides pteronyyssinus,* tree pollens, and a mixture of crops and herb pollens. Three patients with positive prick test results had increased IgE.

One hundred and six patients (28.6%) had a history of medication directed towards treatment of hypertension, diabetes, heart disease, hyperlipidemia, arthralgia, migraine, asthma, epilepsy, goitre, benign prostate hyperplasia, hormonal impairment, or contraception. Changing angiotensin converting enzyme (ACE) inhibitor as antihypertensive medication in two cases and withdrawal of aspirin in one case led to an an improvement in urticaria.

Table 3. A comparison of results of autologuous serum skin test (ASST) with rates of anti-TPO and/or anti-TG antibody positivity

	Anti-TPO and/or anti-TG		
ASST	Negative	Positive	Total
Positive	100 (%80.0)	25 (%20.0)	125 (%100.0)
Negative	13 (%18.1)	59 (%81.9)	72 (%100.0)
P>0.05	113 (%57.3)	84 (%42.6)	197 (%100.0)

Twelve patients (2.3%) had antinuclear antibody (ANA) positivity. One patient with ANA positivity had solar urticaria. Another patient with ANA positivity was diagnosed with systemic lupus erythematosus.

Of the 228 patients with urticaria accompanied by angioedema, 17 (7.5%) had decreased C1 esterase inhibitor levels. Two (0.5%) were found to have hereditary angioedema.

Thyroid function tests showed hypothyroiditis in 13 patients (3.5%) and hyperthyroiditis in four (1.1%). Thirty-three patients (8.9%) had antimicrosomal positivity, 12 patients (3.2%) had antithyroglobulin antibody positivity, and 39 patients (10.5%) had positivity for both antibodies.

One hundred and five out of 150 patients with chronic urticaria underwent ASST (70%), and 20 out of 47 patients with PU (42.6%) had positive test results. Of the 125 patients with ASST positivity, 79 were women and 46 men. The rate of ASST positivity was higher among female patients, though not significantly so (*P*>0.05) (Table 2). Twenty-five patients had positivity for both ASST and at least one thyroid autoantibody (20%). However, there was no significant relation between positivity for ASST and thyroid autoantibody positivity (*P*>0.05) (Table 3).

Of the 354 patients administered provocation tests, 131 (37.0%) had positivity for PU. Ninety-one of the patients with PU were women and 40 were men. Ages ranged between 5 and 74 years, with a mean age of 34.57 ±12.15 years. Duration of the disease ranged from 6 weeks to 30 years, with a mean duration of 3.78 ±5.84 years. Forty-three patients with PU (32.8%) had accompanying angioedema. Of all the patients with PU, 104 (29.4%) had symptomatic dermographism, 10 (2.8%) had acquired cold urticaria, two (0.6%) had hot urticaria, one (0.3%) had solar urticaria, four (1.1%) had symptomatic dermographism and late pressure urticaria, three (0.8%) had symptomatic dermographism and acquired cold urticaria, and one had symptomatic dermographism and aquagenic urticaria (0.3%). Thirteen (3.7%) of the 354 patients had cholinergic urticaria. Six patients with PU, four (1.1%) with symptomatic dermographism, and two (0.6%) with acquired cold urticaria had accompanying cholinergic urticaria (Table 4). Fifteen cases of acquired cold urticaria (4.2%) had a primary disease. Twenty

Table 4. Frequencies of physical urticarias and cholinergic urticaria in the patients with urticaria

	Urticaria	Cholinergic urticaria	SD	Cold urticaria	Hot urticaria	Solar urticaria	SD + pressureurticaria	SD + aquagenicurticaria	SD+cold urticaria	Cholinergic urticariia+ cold urticaria	Cholinergic urticaria + SD
Women	236	4	75	9	1	1	3	0	2	1	1
Men	118	9	29	1	1	0	1	1	1	1	3
Total	354	13	104	10	2	1	4	1	3	2	4
(%)	100.0	3.7	29.4	2.8	0.6	0.3	1.1	0.3	0.8	0.6	1.1

SD: symptomatic dermographism

patients with positivity for ASST (16%) also exhibited PU positivity at provocation tests. Of these 20 patients, 12 (60%) had symptomatic dermographism, three (15%) had cold urticaria, two (10%) had cholinergic urticaria, one (5%) had cholinergic urticaria and cold urticaria, one (5%) had symptomatic dermographism and aquagenic urticaria, and one (5%) had symptomatic dermographism and cold urticaria.

Three hundred and sixty-four patients (72.8%) reported one or more of the following items in the questionnaire concerning causes of urticaria: stress, an event strongly affecting the individual, nervousness-restlessness-anxiety, sadness-unhappiness-pessimism, sleep disorders, or a problem requiring professional help. These patients were interviewed about the items they confirmed. Psychiatric consultations were requested for 105 patients (29%). Of these 105, 60 (57.1%) were recommended medical treatment. The most frequent diagnoses were depression (16.4%), generalized anxiety disorder (15.1%), and adaptation disorder (9.6%).

Skin biopsy was performed in 14 cases (2.8%) in which urticaria could not be differentiated from urticarial vasculitis. Five (35.7%) had urticarial vasculitis and five (35.7%) had urticaria, but four (28.6%) exhibited no important features at histological examination.

DISCUSSION

Although clinically different subtypes of chronic urticaria have been described by the EAACI, GA^{2}LEN, EDF and WAO, a patient may have two or more subtypes of the disease. Although PUs exhibit the characteristics of chronic urticaria, they fall under a different category since their occurrence depends on the presence of physical factors. Since acute and chronic urticarias develop spontaneously without a specific outer stimulus, these are categorized as spontaneous urticaria (1,2,9).

No specific triggering factors can be detected in approximately 75% cases of chronic urticaria (5). The causes of these urticarias are still unclear, and there are still problems with diagnostic investigation and treatment, which are mostly caused by PUs. PUs, except for late pressure urticaria, do not last for more than two hours. However, lesions of chronic idiopathic urticaria (CIU) and chronic autoimmune urticaria (CAU) may persist for 4-36 hours (4). Since PUs are frequently accompanied by CIU, it is important to perform appropriate tests to diagnose them (9-11). It is also of particular importance to distinguish urticarial vasculitis from CIU. Absence of pigmentation after chronic urticaria lesions have healed is also important in terms of differential diagnosis (10).

In agreement with the literature, most of the patients with chronic urticaria in this study were women (260 women compared to 110 men), and the mean duration of the disease was 3.6 ± 4.9 years (5,6).

Although infections, metabolic and hormonal disorders, malignant diseases, and emotional factors have been incriminated in the etiology of chronic urticaria, there is no strong evidence for these (12,13). There have been many studies of comorbidity of chronic urticaria and chronic infections. However, there is no evidence that infectious pathogens lead to chronic urticaria (13,14). In this study, 29 patients (7.8%) had sinusitis, 26 (7%) had urinary infection, and two (0.5%) had upper respiratory tract infection caused by β haemolytic streptococci. Out of 11 female patients, 10 (2.7%) had vaginitis and one (0.3%) had pelvic inflammatory disease. Urticaria subsided in only two patients after treatment for vaginitis.

Parasitic infections may cause urticarial rash, especially in areas where parasitoses are endemic (4,10,14,15). In this study, 31.6% of subjects had parasites. Urticaria subsided in only four patients (1.1%) after treatment for parasitic infections.

Although urticaria has been associated with hepatitis C infection, no significant increase has been observed in the numbers of cases in which these two conditions are comorbid in large series (16). In the present study, 14 patients (3.8%) had hepatitis B and six (1.6%) had hepatitis C.

Apart from infections, non-infectious chronic inflammatory conditions are also implicated in the etiology of chronic urticaria. These conditions include gastritis, reflux esophagitis, inflammation of the gallbladder and the bile ducts, and more rarely autoimmune diseases such as systemic lupus erythematosus and neoplasia (13,17). In the present study, 10 patients (2.7%) had gastritis, three (0.8%) had reflux esophagitis, two (0.5%) had cholelithiasis, one (0.3%) had systemic lupus erythematosus, and six (1.6%) had internal malignity (one with brain tumour, one with thyroid lymphoma, one with colonic carcinoma, one with prostatic carcinoma, and two with breast carcinoma).

The incidence of atopia in patients with chronic urticaria is not as high as that in the general population, and IgE levels are either normal or slightly higher than normal in most patients (18). In this study, 25 out of 39 patients with a history of atopia (10.5%) had high levels of IgE.

Although drugs are less frequently implicated in chronic urticaria, it is important to remember they may be causative factors (19). In one study, 9% of 220 patients were found to have chronic urticaria due to medications and/or angioedema (20). In the present study, 28.6% of patients had a history of various medications. However, urticaria improved in only three cases after the suspect medication was withdrawn. Patients with chronic urticaria should be asked whether they take ACE inhibitors, aspirin, and non-steroidal anti-inflammatory drugs.

Comorbid chronic urticaria and angioedema have been reported in approximately 50% of cases (21). In the present study, chronic urticaria was accompanied by angioedema in 61.6% of patients. Angioedema developing due to hereditary deficiency of C1 esterase inhibitors accounts for less than 0.1% of all cases of angioedema, and C4 levels are always low in these cases (22). In the present study, two patients (0.5%) had hereditary angioedema and low C4 levels, which is consistent with the literature (10,22).

Absence of any conditions likely to cause chronic urticaria in most cases suggests that it may be an autoimmune disease (23-25). This idea is also supported by the evidence that CIU is accompanied by autoimmune thyroiditis and, more specifically, the presence of IgG antibodies developing against thyroglobulin and peroxidise (4,12,26,27). Individuals with chronic urticaria have been shown to have higher serum concentrations of antithyroid antibodies than the normal population (24). The incidence of antithyroid antibodies in cases of chronic urticaria ranges from 15% to 24% (4). Leznoff and Sussman (28) reported thyroid autoimmunity in 14.4% of 624 patients with chronic urticaria, compared to an incidence of 6% in the general population. In our study, 22.7% of patients exhibited positivity for one or more antithyroid autoantibodies, which is quite similar to the level reported in the literature.

Recent studies have found IgG1 and IgG3, histamine releasing circulating autoantibodies specific to the α subunit of the high affinity IgE receptor (FcεRI), in approximately 30%-60% of patients with chronic urticaria, and functional anti IgE antibodies at lower levels. These antibodies can in practice be detected using ASST, an inexpensive and reliable method. Sensitivity and specificity of ASST have both been reported at 80%. Apart from ASST positivity, various factors which lead to histamine release have been identified in patients with chronic autoimmune urticaria. When donor basophiles are incubated with patient serum, the serum of these patients may cause histamine release from the donor basophiles. ELISA and immunoblot techniques have helped to show autoantibodies to FcεRI, not only in patients with chronic urticaria, but also in the normal population. These techniques do not seem to be sufficiently specific to detect functional autoantibodies in chronic urticaria. The gold standard for detecting functional autoantibodies is therefore in vitro donor basophile histamine release. However, this is a lengthy procedure and difficult to perform. Since we could not perform this technique, we used ASST and determined positivity in 63.5% of patients, similar to the level reported in the literature (22,29-31).

In recent years, higher rates of antimicrosomal antibody positivity and abnormal thyroid function tests in patients with autoantibodies triggering histamine release have attracted the attention of researchers. Although the incidence of thyroid autoimmune disease in CIU does not differ from that of the general population, it should be noted that thyroid autoantibodies may aggregate in patients with ASST positivity, in that they indicate antibodies triggering histamine release (32,33). We therefore investigated whether ASST results were associated with antithyroid anti-

body positivity in patients with chronic urticaria. Out of 125 patients with ASST positivity, 25 (20%) exhibited positivity for at least one thyroid autoantibody, although this was statistically insignificant ($P>0.05$).

PU is responsible for 20-31% of all cases of urticaria. According to more recent studies, this rate has increased to 71-80% (6,8,12,22). In the current study, 37% of patients had PU. The most frequent type of PU was symptomatic dermographism, at 29.4%. These figures are consistent with the literature. It has been reported that only 5% of patients with cold urticaria may have secondary acquired cold urticaria (22). None of the patients in this study had secondary acquired cold urticaria. Solar urticaria is a rare clinical picture and may coexist with systemic lupus erythematosus and erythropoietic protoporphyria (6,12). Only one patient in this study, with no pathological conditions except for ANA positivity, was found to have solar urticaria.

ASST positivity accompanied by PUs in 16% of the patients in this study indicates that PUs may coexist with autoimmune urticaria.

Psychological factors may also be involved in cases of chronic urticaria. Some of the conditions diagnosed as CIU may be due to psychogenic factors. In fact, it is impossible to clearly define psychogenic urticaria. Many chronic diseases can be aggravated by emotional stress. It may be beneficial to provide psychiatric support for patients with suspected CIU and considerable emotional stress (6,12). Jáuregui et al. reported that chronic urticaria has an adverse impact on quality of life (34). In this study, of the 364 patients with chronic urticaria reporting feeling stressed (72.8%), 105 (29%) were examined by a psychiatrist and 60 (16.5%) were recommended psychiatric treatment.

CONCLUSION

In general, cases of urticaria or angioedema have clinical pictures which are not difficult to recognize with detailed history and examination. The problem is that determining the causes of urticaria and finding the appropriate treatment in all conditions can be difficult. Therefore, appropriate diagnostic tests should be conducted to detect PUs and chronic autoimmune urticaria. An autoimmune mechanism and physical stimuli play an important part in the development of urticarias.

References

1. Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Giménez-Arnau A, *et al.* EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. Allergy 2009;64:1417-26.
2. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, *et al.* The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy 2014;69:868-87.
3. Grattan CEH, Sabroe RA, Greaves MW. Chronic urticaria. J Am Acad Dermatol 2002;46:645-57.
4. Kaplan AP. Chronic urticaria: pathogenesis and treatment. J Allergy Clin Immunol 2004;114:465-74.
5. Ortonne JP. Chronic idiopathic urticaria for the generalist. Eur J Int Med 2003;14:148-57.
6. Grattan CEH, Black AK. Urticaria and angioedema. In: Bologna JL, Jorizzo JL, Rapini RP, editors. Dermatology. 2nd ed. Edinburgh, Scotland: Mosby; 2008. p. 261-76.
7. Liutu M, Kalimo K, Uksila J, Kalimo H. Etiologic aspects of chronic urticaria. Int J Dermatol 1998;37:515-9.
8. Çam Ö, Altunay İK, Köşlü A. The incidence of physical urticarias in the patients with chronic urticaria. Türkderm 2002;36:30-3.
9. Abajian M, Schoepke N, Altrichter S, Zuberbier T, Maurer M. Physical urticarias and cholinergic urticaria. Immunol Allergy Clin North Am 2014;34:73-88.
10. Greaves M. Chronic urticaria. J Allergy Clin Immunol 2000;105:664-72.
11. Grattan CEH. The urticaria spectrum: recognition of clinical patterns can help management. Clin Dermatol 2004;29:217-21.
12. Kaplan AP. Urticaria and angioedema. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, editors. Fitzpatrick's Dermatology in General Medicine. 7th ed. New York: Mc Graw Hill; 2008. p. 330-43.
13. Saini SS. Chronic spontaneous urticaria: etiology and pathogenesis. Immunol Allergy Clin North Am 2014;34:33-52.
14. Tedeschi A, Airaghi L, Lorini M, Asero R. Chronic urticaria. A role for newer immunomodulatory drugs? Am J Clin Dermatol 2003;4:297-305.
15. Hameed DM, Hassanin OM, Zuel-Fakkar NM. Association of Blastocystis hominis genetic subtypes with urticaria. Parasitol Res 2011;108:553-60.
16. Doutre MS, Beylot BM, Beylot C. Urticaria and hepatitis C infection. Br J Dermatol 1998;138:194.

17. Zuberbier T. Urticaria. Allergy 2003;58:1224-34.
18. Aytekin S, Türkmen H. Investigation of autologous serum skin test and etiological factors in 31 patients with chronic urticaria. T Klin Dermatol 2001;11:141-5.
19. Shipley D, Ormerod AD. Drug-ınduced urticaria: Recognition and treatment. Am J Clin Dermatol 2001;2:151-8.
20. Kozel MM, Mekkes JR, Bossuyt PM, Bos JD. The effectiveness of a history-based diagnostic approach in chronic urticaria and angioedema. Arch Dermatol 1998;134:1575-80.
21. Sabroe RA, Greaves MW. The pathogenesis of chronic idiopathic urticaria. Arch Dermatol 1997;133:1003-8.
22. Su Ö, Onsun N, Atılganoğlu U, Kural YB, Aygın S, Konuk E. Algorhythmic approach to the etiopathogenesis of chronic urticaria: practical benefits. Türkderm 2002;36:24-8.
23. Dalal I, Levine A, Somekh E, Mizrahi A, Hanukoglu A. Chronic urticaria in children: expanding the "autoimmune kaleidoscope". Pediatrics 2000;106:1139-41.
24. Verneuil L, Leconte C, Balet JJ, Coffin C, Laroche D, Izard JP, *et al.* Association between Chronic urticaria and thyroid autoimmunity: A prospective study involving 99 patients. Dermatology 2004;208:98-103.
25. Heymann WR. Chronic urticaria and angioedema associated with thyroid autoimmunity: Review and therapeutic implications. J Am Acad Dermatol 1999;40:229-32.
26. Rottem M. Chronic urticaria and autoimmune thyroid disease: is there a link? Autoimmunity reviews 2003;2:69-72.
27. Magen E, Mishal J. The effect of L-thyroxine treatment on chronic idiopathic urticaria and autoimmune thyroiditis. Int J Dermatol 2012;51:94-7.
28. Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. J Allergy Clin Immunol 1989;84:66-71.
29. Sabroe RA, Greaves MW. Chronic idiopathic urticaria with functional autoantibodies: 12 years on. Br J Dermatol 2006;154:813-9.
30. Fusari A, Colangelo C, Bonifazi F, Antonicelli L. The autologous serum skin test in the follow-up of patients with chronic urticaria. Allergy 2005;60:256-8.
31. Aydın F, Pancar Yüksel E. Diagnosis and treatment of autoimmune urticaria. Turkiye Klinikleri J Dematol-Special Topics 2012;5:16-9.
32. Emre S, Özçelik S, Akyol M. The relationship between autologous serum skin test and thyroid antibodies in patient with chronic idiopathic urticaria. T Klin Dermatol 2004;14:149-55.
33. Turkoglu Z, Zindanci I, Turkoglu O, Can B, Kavala M, Tamer G, *et al.* Skin autoreactivity in Hashimoto's thyroiditis patients without urticaria: autologous serum skin test positivity correlation with thyroid antibodies, sonographical volume and grading. Eur J Dermatol 2012;22:345-50.
34. Jáuregui I, Ortiz de Frutos FJ, Ferrer M, Giménez-Arnau A, Sastre J, Bartra J, *et al.* Assessment of severity and quality of life in chronic urticaria. J Investig Allergol Clin Immunol 2014;24:80-6.