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Clinical features of chronic urticaria in aging population

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Abstract

Background: Different clinical features of skin diseases have been addressed between aging patients and non-aging patients. However, data focusing on the clinical features of chronic urticaria (CU) in aging patients especially in the Asian population are still limited.

Objective: This study aimed to investigate the clinical characteristics of CU in aging and non-aging patients in the Asian population.

Methods: Case records of 1622 CU patients attending the Urticaria Clinic, Department of Dermatology, Siriraj Hospital, Mahidol University, Thailand between 2000 and 2013 were retrospectively reviewed. All CU patients older than 60 years were recruited. Twice the number of CU patients who were non-aging were enrolled using a systematic sampling method.

Results: Of the 1622 CU patients, 67 (4.1%) were aging patients. From these, 134 non-aging patients with CU were recruited. The majority of patients for both groups were female, with 67.2% and 77.6% of the aging and non-aging groups, respectively. In both groups, the most common cause of CU was chronic spontaneous urticaria. In the aging group, positive autologous serum skin test, anti-thyroid antibodies and antinuclear antibodies were found more commonly than in the non-aging group, without a statistically significant difference. The mean duration of the disease tended to be shorter in the aging group.

Conclusion: Our study showed that CU in aging patients was uncommon (4.1%). Aging patients with CU seemed to have shorter disease duration and higher percentages of autoantibodies than non-aging patients with CU without a statistically significant difference.

Keywords: Asian population, chronic urticaria, aging, clinical characteristics, laboratory investigations

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Introduction

Currently, geriatric medicine is more interesting and challenging because the proportion of aging patients has gradually increased around the world. The United Nations' World Population Ageing Report considers people aged 60 years or older to be aging people[1] while the World Health Organization Scientific Group on the Epidemiology of Aging defines people aged 65 or older as the elderly population.[2] Aging and non-aging patients can have differences in the clinical manifestations of several diseases such as psoriasis,[3] herpes zoster,[4] and urticaria.[5,6] Polypharmacy (multiple medication usages and/or the administration of more clinically indicated medications)[7] and the aging process may interfere with pharmacokinetics and pharmacodynamics, resulting in different responses to treatments.[8]

Chronic urticaria (CU) is a common skin disease characterized by the presence of itchy wheals with or without angioedema lasting for at least six weeks. In general, CU occurs most frequently after adolescence with the highest incidence in young adults.[9] To the best of our knowledge, data focusing on the clinical features of CU in the geriatric population are limited. This study aimed to investigate the clinical characteristics of CU in the aging Thai population, which is an Asian population, and to compare these data with those of the non-aging population and with previous studies.

Methods

This study has been approved by the Siriraj Institutional Review Board, Siriraj Hospital, Mahidol University, Bangkok, Thailand. Case records of 1,622 patients attending the Urticaria Clinic, Department of Dermatology between the years 2000 and 2013 were retrospectively reviewed. CU was defined as recurrent urticaria occurring at least twice a week for at least six weeks. In our study, patients with CU age 60 years or older were classified as aging patients and recruited to the study.[2,10] Subsequently, twice the number of patients aged less than 60 years old were selected by a systematic sampling method. A complete history of possible causes, physical examination, necessary tests and laboratory investigations were performed in all patients. Screening for food allergy or food intolerance was investigated by taking a thorough medical history, skin prick testing and an elimination diet for 3 weeks.[5,11,12] Oral food challenge tests were performed if necessary. All suspected drugs used were discontinued or replaced with chemically unrelated drugs. For physical urticaria, provocative tests were done as follows:[13]

(a) Dermographism was evaluated by firm stroking of the skin using a dermographometer with a pressure of 4900 gm/cm^2, which induced linear itchy wheals within minutes.

(b) Delayed pressure urticaria was diagnosed by using sandbags joined by a rope weighing 15 pounds each placed over one shoulder for 15 minutes, which resulted in a palpable wheal at the application site two to eight hours later.

(c) Cold urticaria was tested by application of an ice cube in a thin plastic bag to the skin of the forearm for 20 minutes which caused whealing to occur within 15 minutes at the test site, on rewarming the skin.

(d) Cholinergic urticaria was performed by asking the patient to run on the spot to the point of perspiration. A positive response was defined by subsequent pruritic erythematous punctuate whealing, within 5–15 minutes.

(e) Solar urticaria was evaluated using a photo test and subsequently confirmed by exposure to natural sunlight.

Laboratory investigations included complete blood count, urinalysis, erythrocyte sedimentary rate, stool examination and other investigations that were necessary for the individuals, including urea nitrogen, creatinine, aspartate aminotransferase, alanine transferase, alkaline phosphatase, bilirubin, total protein, albumin, hepatitis B surface antigen, anti-hepatitis C virus, free T3, free T4, thyroid stimulating hormone using immunoassay method (Cobas® by Roche Diagnostics, Mannheim, Germany), anti-thyroid autoantibodies (anti-thyroglobulin and anti-thyroid peroxidases; chemiluminescense immunoassay; Abbot, USA), antinuclear antibodies, cryoglobulins, serum complement level, chest and sinus X-ray studies. The autologous serum skin test (ASST) was performed by an intradermal injection of 50 µl of undiluted autologous serum into the volar aspect of the forearm together with simultaneously injected controls including saline and histamine 10 µg/ml. The test was positive at 30 minutes if the serum-injected site manifested a wheal with a diameter at least 1.5 millimeters greater than that of the saline wheal.[14]

After a thoroughly taken history, physical examination and investigations, patients were classified according to the European Academy of Allergology and Clinical Immunology guidelines as chronic spontaneous, physical urticaria and other urticaria types.[15] Descriptive statistics (e.g., mean, median, minimum, maximum, frequency and percentages) were used to describe the demographic data, possible causes and laboratory findings. Categorical variables were compared between the two groups by using the χ^2 test. Because some patients were lost to follow up, to determine the probability of symptom resolving at each time point, the Kaplan-Meier survival curve which showed the probability of remission was applied. All analyses were 2-sided, and a P value of less than 0.05 was considered statistically significant. All statistical data analyses were performed using SPSS for Windows version 18 (SPSS, Chicago, IL, USA).

Results

Of 1,622 CU patients who attended the Urticaria Clinic, Department of Dermatology over a 13 year-period, 67 patients (4.1%) with CU were aging patients. One hundred and thirty-four non-aging patients with CU were enrolled using a systematic sampling method. Demographic data of both groups were not statistically significantly different (**Table 1**). The majority of the patients with 67.2% and 77.6% of the aging and non-aging groups respectively were female. The mean duration of urticarial symptom was 207 days in the aging group and 211 days in the non-aging group. Allergic rhinitis was the most common atopic disorder reported in this cohort of patients. The possible causes of CU are shown in **Table 2**. Chronic spontaneous urticaria (CSU) was the most common cause for patients in both groups. Other possible causes included physical urticaria (symptomatic dermographism, cold urticaria, and delayed pressure urticaria), other urticaria types (cholinergic urticaria), infection (chronic paronychia), hyperthyroidism and atopy. When comparing between the groups, physical urticaria was more commonly detected in the non-aging group; however, there was no statistically significant difference. The term CSU, which was used as a label after excluding physical or other identifiable causes (not including autoimmune urticaria), was found in 94% (63/67) and 90.3% (121/134) of the aging and non-aging patients with CU, respectively.

Abnormal laboratory findings are shown in **Table 3**. Positive ASST was the most common abnormal laboratory finding in both groups and was detected more commonly in the aging group, but there was no statistically significant difference to the non-aging group. Positive anti-thyroglobul in antibodies were the second most common abnormal laboratory finding in the aging group. **Figure 1** demonstrates the duration of the disease by Kaplan-Meier curve. After one year of the onset of the symptoms, 18.8% and 17.2% of aging and non-aging patients, respectively, were free of symptoms. The mean duration of the disease tended to be shorter in the aging group (2.21 vs 5.11 years). However, there was no statistically significant difference.

Table 1. Demographic of patients with chronic urticaria in aging and non-aging groups

Characteristics	Aging patients (n=67)	Non-aging patients (n=134)	p-value
Sex			0.126
Female (%)	67.2	77.6	
Male (%)	32.8	22.4	
Mean age (years, range)	67 (60-83)	35.6 (15-59)	<0.001
Mean duration of symptoms (days)	207	211	0.859
Associated with angioedema (%)	23.9	28.0	0.612
Personal history of atopy			0.613
Allergic rhinitis (%)	22.4	18.8	0.577
Asthma (%)	1.5	5.3	0.272
Allergic conjunctivitis (%)	0	1.5	0.552
Atopic dermatitis (%)	0	0.8	1.0
Family history of atopy			0.146
Allergic rhinitis (%)	7.5	16.5	0.084
Asthma (%)	3.0	1.5	0.603
Atopic dermatitis (%)	1.5	0.8	1.0
Allergic conjunctivitis (%)	0	0.8	1.0

Table 2. Possible causes/associated factors of chronic urticaria in aging and non-aging groups

Possible causes/associated factors	Aging patients (n=67)	Non-aging patients (n=134)	p-value
Chronic spontaneous urticaria (%)	94.0	90.3	0.690
Physical urticaria			
Symptomatic dermographism (%)	3.0	3.0	
Cold contact urticaria (%)	-	0.7	
Delayed pressure urticaria (%)	-	2.2	
Other urticaria types			
Cholinergic urticaria (%)	-	1.5	
Infection: chronic paronychia (%)	1.5	-	
Hyperthyroidism (%)	1.5	1.5	
Atopy * (%)	-	0.7	

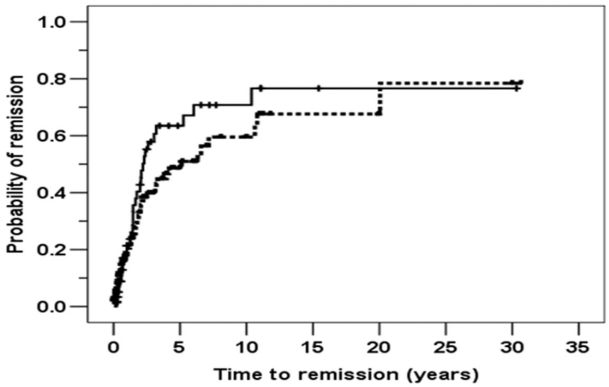
* Urticaria wheals were frequently accompanied by an exacerbation of asthma, allergic rhinitis and atopic dermatitis

Table 3. Abnormal laboratory investigations in patients with chronic spontaneous urticaria

Laboratory findings	Aging patients (n=63)	Non-aging patients (n=121)	p-value
Positive ASST (%)	58.3	33.3	0.110
Positive antithyroglobulin antibodies (%)	33.3	6.3	0.061
Elevated ESR (%)	28.6	32.1	0.805
Positive antithyroid peroxidase antibodies (%)	22.2	12.5	0.597
Positive antinuclear antibodies (%)	21.7	18.6	0.765
Abnormal urinalysis* (%)	16.2	9.1	0.346
Positive HBsAg (%)	13.3	0	0.089
Leukocytosis (%)	6.0	6.0	1.0
Abnormal stool examination† (%)	3.0	10.9	0.248
Eosinophillia (%)	0	0	-
Positive Anti-HCV Ab (%)	0	0	-

Abbreviations: ASST, autologous serum skin test; ESR, erythrocyte sedimentation rate, HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus
* All the patients had transient pyuria (WBC range from 5-20/HPF) with no clinical significance.
† All the patients had *Blastocystis hominis* in stool examination and after treatment with antiparasitic drugs, urticaria still persisted.

Figure 1. A Kaplan–Meier curve demonstrated the duration of the diseases of aging and non-aging patients with chronic spontaneous urticaria.



Discussion

In our study, demographic data regarding sex, mean disease duration, association with angioedema, and family and personal histories of atopy between the aging and non-aging groups were not different. CSU was the most common diagnosis for both groups. It should be noted that a cohort study of 12,720 patients from Taiwan found that patients with CU were at increased risk of cancer, especially hematologic malignancy. The relative risk of cancer was highest among patients aged between 20 and 39 years (5.8, 95%CI = 4.1-8.1) and gradually decreased over time.[16] Patients aged 60-79 years and ≥ 80 years had a relative risk of malignancy of 1.9 (95%CI = 1.7-2.1) and 1.3 (95%CI = 1.0-1.7), respectively. Most cancers were detected within the first year of CU diagnosis. However, the present study and that of Magen et al. were not able to demonstrate that malignancy was a cause or associated factor of aging CU patients. It is possible that both studies had a limited number of patients.

Table 4. Comparison of data between Thai aging chronic spontaneous urticaria (CSU) patients and those of Magen et al.[5] and Ga-Young Ban et al.[6]

Characteristic	Present Study (n=63)	Magen et al. [5] (n=92)	Ga-Young Ban et al. [6] (N=37)
Prevalence of CSU in aging (%)	4.1	9.4	4.5
Female (%)	67.2	46.7	51.4
Age (years)	67.3 ± 5.0	71.9 ± 6.7	65.7 ± 5.9
Ethnic	Asians	Non-Asians	Asians
Personal history of atopy			
Allergic rhinitis (%)	22.4	8.7	29.7
Asthma (%)	1.5	2.2	19.4
Allergic conjunctivitis (%)	0	NA	5.9
Atopic dermatitis (%)	0	4.2	37.8
ASST positive (%)	58.3	18.1	NA
Wheals and angioedema (%)	23.9	14.1	NA
CSU remission at 12 months (%)	21	42.3	NA
CSU (%)	94.0	72.2	NA
Physical urticaria (%)			
Symptomatic dermographism (%)	3.0	4.8	NA
Solar urticaria (%)	-	0.8	NA
Delayed pressure urticaria (%)	-	1.6	NA
Other urticaria types (%)			
Cholinergic urticaria (%)	-	2.4	NA
Infection: chronic paronychia (%)	1.5	-	NA
Hyperthyroidism (%)	1.5	-	NA
Papular urticaria/insect bites (%)	-	0.8	NA
Parasitic infestations (%)	-	4.0	NA
Collagen vascular diseases (%)	-	3.2	NA
Drugs (%)	-	8.9	NA
Laboratory			
WBC count (cell/mm^3)	6.8±2.3	7.8±4.9	NA
Leukocytosis (%)	6.0	NA	NA
Eosinophils (cell/mm^3)	0.16±0.16	0.42±0.20	NA
Eosinophillia (%)	0	NA	NA
Total IgE (U/mL)	NA	109.3±56.4	138.4 ± 136.4
Elevated ESR (%)	28.6	NA	NA
C-reactive protein (mg/L)	NA	4.69±3.74	NA
TSH (μg/dL)	1.25±1.04 ‡	2.79±1.01§	NA
Positive antithyroglobulin Ab (%)	33.3	NA	17.4
Positive antithyroid peroxidase Ab (%)	22.2	NA	12.5
Positive antinuclear antibodies (%)	21.7	NA	NA
Positive HBsAg (%)	13.3	NA	NA
Positive Anti-HCV Ab (%)	0	NA	NA
C3 (g/L)	NA	1.27±0.39	NA
C4 (g/L)	NA	0.33±0.16	NA
sIgE to SEA (%)	NA	NA	14.3
sIgE to SEB (%)	NA	NA	14.3
sIgE to TSST-1 (%)	NA	NA	12.0

Abbreviations: CSU, Chronic spontaneous urticaria; WBC, white blood cell; Ig, immunoglobulin; ESR, erythrocyte sedimemtation rate; TSH, thyroid stimulating hormone; Ab, antibodies; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; sIgE, specific immunoglobulin; SEA, staphylococcal enterotoxin A; SEB, staphylococcal enterotoxin B; TSST-1, toxic shock syndrome toxin-1; NA, not available;
‡using immunoassay method (cobas® by Roche Diagnostics, Mannheim, Germany), § paper did not describe the method.
Note: A patient older than 60 years was defined as an aging patient in the present study and Ga-Young Ban et al.'s study while Magen et al. defined a patient older than 65 years as an aging patient.

There were no statistically significant differences of the abnormal laboratory findings between both groups. However, aging patients with CU tended to have higher percentages of positive ASST, positive anti-thyroglobulin antibodies and positive anti-thyroid peroxidase antibodies in comparison with non-aging patients with CU. It should be noted that most of the patients with positive thyroid autoantibodies in our study were euthyroid status. Only two patients with positive anti-thyroglobulin antibodies had hyperthyroidism (one patient in each group). In a study of a healthy Thai population, anti-thyroglobulin antibodies were found more commonly in the aging population (7%) than the younger age group (1.4%), while the percentages of positive anti-thyroid peroxidase antibodies were 2.6% and 2.3% in aging and non-aging patients, respectively.[17] Our study showed that aging patients with CU had a higher percentage of thyroid autoantibodies, especially anti-thyroglobulin antibodies, than non-aging patients with CU and healthy controls. Ramos-Casals et al. reported that aging is associated with the increased production of autoantibodies, resulting in an increased incidence of autoimmune diseases in aging patients.[18] Therefore, we proposed that an increase in the production of autoantibodies in the aging process may be the reason for the higher percentages of autoantibodies in the aging patients with CU.

Although there were sparse data focused on the clinical and laboratory characteristics of CSU in the aging population, data regarding CSU in 92 Israeli and 37 Korean geriatric patients have been reported by Magen et al. and Ga-Young Ban et al., respectively.[5,6] We summarized and compared the data from their studies with ours, as shown in **Table 4**. The prevalence of CSU in aging Asian patients seemed to be lower than in aging Caucasian patients. In contrast to the study by Magen et al., our study showed that female gender, a higher percentage of wheal-associated angioedema, and a higher percentage of positive ASST were more commonly detected in the aging patients with CU. This might be explained by the immunogenic differences between Oriental and Caucasian populations.[19-21] On the other hand, our study and that of Magen et al. showed similar findings, namely that CSU followed by physical urticaria was the most common cause of aging patients with CU. Ga-Young Ban et al. emphasized the relationship between atopic dermatitis (AD) and CU in aging patients. However, there was no significant relationship between AD and aging CU patients in our study and the study by Magen et al.

It should be noted that our study had some limitations. Firstly, there was missing information due to the retrospective nature of the study. Secondly, the number of the aging patients in our study might be too small to demonstrate significant findings. Further studies with a larger number of patients are warranted to conclude clinical characteristics of CU in aging patients.

In conclusion, clinical features including the demographic data, possible causes or associated factors, abnormal laboratory findings and clinical courses of CU patients in this study were not statistically significantly different between the aging and non-aging groups. However, aging CU patients had the tendency to have shorter disease duration, higher percentages of anti-thyroglobulin antibodies, and positive ASST in comparison with the non-aging CU patients.

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