

ORIGINAL ARTICLE

Cholinergic urticaria: More than a simple inducible urticaria

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ABSTRACT

Background: Cholinergic urticaria (ChU) is characterized by small wheals induced by an elevated core temperature. Its pathomechanism and various aspects of its clinical manifestations are still poorly understood. This study aimed to evaluate the spectrum of symptoms and signs of ChU in Korean patients.

Methods: We retrospectively reviewed the medical records of patients diagnosed with ChU.

Results: Among 203 patients (188 male and 15 female), 29 (14%) complained only of an itching or burning sensation without visible skin eruption. The prevalence of ChU was highest in patients in their twenties (56%), while most patients first developed their symptoms during their teens (65%). Patients with a visible skin eruption showed better responses to antihistamines than those without skin lesions.

Conclusions: Physicians should consider the varying manifestations of ChU, including cholinergic pruritus and erythema as minor variants, to provide better management of ChU.

Key words: cholinergic erythema, cholinergic pruritus, cholinergic urticaria, epidemiology, sweating.

INTRODUCTION

Cholinergic urticaria (ChU) is characterized by small and pruritic wheals surrounded by flares upon an elevation in body temperature, such as after physical exercise, a hot bath or emotional stress.¹ In most cases the diagnosis is straightforward and can be achieved via simple provocation with exercise. However, it has become clear that the clinical manifestations of ChU are more heterogeneous than previously thought.² The mechanism of ChU pathogenesis is still being explored, particularly in relation to perspiration. Despite several reports on the prevalence of ChU in various countries and ethnicities, data on the wide spectrum of ChU manifestations have been insufficient. Accordingly, this study aimed to outline the symptoms and signs of ChU in Korean patients.

PATIENTS AND METHODS

Participants

A total of 203 patients diagnosed with ChU by an exercise provocation test from January 2005 to March 2015 at the Yonsei University Hospital Dermatology Clinic in Seoul, Korea, were included. The study was performed in accordance with the guidelines of the International Conference on Harmonization for Good Clinical Practice, as stipulated in the Declaration of Helsinki. Local ethics committee approval was obtained.

Assessment

The medical records of the study participants were retrospectively reviewed. The collected data included clinical information, such as the patients' sex, age, duration of the symptoms, age of onset, comorbidity, relation to perspiration, responsiveness to treatment, and laboratory test results, including a complete blood count with differential, routine chemistry, and the multiple allergen simultaneous

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Abbreviations:

AD	atopic dermatitis
ANA	anti-nuclear antibody
ChU	cholinergic urticaria
MAST	multiple allergen simultaneous test

test (MAST) assay. Responsiveness to treatment with antihistamines was evaluated as poor, fair and good: a poor response was defined as an absent to slight improvement, thus requiring different treatment; a fair response was defined as a moderate improvement with less extensive and less frequent symptoms, which were tolerable but not completely cleared; and a good response was defined as the complete or near complete clearing of the symptoms.

Statistics

Statistical analysis was performed using IBM SPSS Statistics for Windows, vers. 20.0 (IBM, Armonk, NY, USA). A Student's *t*-test was used to compare the patient's age and duration of ChU between groups determined by sex and the presence of skin eruption. The chi square test and Fisher's exact test were conducted to compare the age of onset, comorbidity, responsiveness to treatment and relation to perspiration. All *P* values < 0.05 (two-tailed tests) were considered statistically significant.

RESULTS

Grouping of the patients

A total of 203 patients (188 male and 15 female) were included in the study (Table 1). Interestingly, 29 patients (14%) complained only of itching or a burning sensation without a visible skin eruption (e.g., pinhead-sized papular wheals) after provocation through exercise. Hence, the patient grouping for comparing epidemiological characteristics was done in two ways: by sex and by the presence of skin eruption (Tables 2,3) respectively.

Age, onset, and duration of ChU

The mean age of the patients with ChU was 22.6 ± 6.7 years, with the highest prevalence seen in patients in their twenties (114, 56%), followed by teenagers (70, 35%). The mean duration of ChU was 30.4 ± 28.6 months (Table 1). When participants were divided into five groups by the duration of the condition (in months, 0–12, 12–35, 36–59, 60–119 and > 120), about 25% had had ChU for longer than 5 years. Symptom onset was most common in the second decade of life (65%), followed by the third (28%), fourth (6%) and fifth (2%) decades. Age, duration of urticaria and distribution of onset age were not significantly different according to sex or the presence of skin eruption.

Morphology of skin eruption

Most of the patients with a skin eruption (156, 90%) had pinhead-sized wheals, while some had an erythematous halo (Fig. 1a). Some patients had only follicular wheals without an associated halo (Fig. 1b). Meanwhile, 12 patients (6%) mainly showed macular or patch-like erythema (Fig. 1c). A total of 29 patients (14%) reported only subjective burning, stinging and itching without visible skin eruption, even after vigorous exercise (Fig. 1d).

Table 1 Patients' epidemiology data

	Data
Sex	
Male	188 (93)
Female	15 (7)
Age at first hospital visit (in years), Mean (range)	22.6 ± 6.7 (14–50)
10–19	70 (35)
20–29	114 (56)
30–39	14 (7)
40–49	4 (2)
50–59	1 (1)
Age of onset (year)	
10–19	131 (65)
20–29	56 (28)
30–39	12 (6)
40–49	4 (2)
Duration (month), Mean (range)	30.4 ± 28.6 (0.5–133)
0–12	54 (27)
12–35	62 (31)
36–59	37 (18)
60–119	42 (21)
> 120	8 (4)
Absence of visible skin eruption	29 (14)
Co-morbidities	
Atopic dermatitis	16 (8)
Allergic rhinitis	4 (2)
Asthma	2 (1)
Crohn's disease	3 (2)
Dermographism	7 (3)
Others [†]	4 (2)
Relation to perspiration	15 (7)
Responsiveness to antihistamine treatment	
Poor	46 (23)
Fair	77 (38)
Good	80 (39)
House dust mite allergy in MAST	14 (7)

[†]n: penicillin allergy 1, Graves disease 1, Seizure 2. Values are presented as mean $\pm$ standard deviation (range) or number (%). MAST, multiple allergen simultaneous test.

Responsiveness to treatment

More than 70% of the patients showed a fair or good response to antihistamine therapy. While more female (93%) than male (75%) patients had a fair or better response to treatment, this difference was not statistically significant. Patients with a visible skin eruption exhibited better responses to antihistamine therapy than those without a skin eruption ($P < 0.01$). While only 18% of the patients with skin eruption showed a poor response, 48% of the patients without a skin eruption exhibited a poor response to antihistamine therapy. Patients with a poor response to antihistamine therapy were treated with additional systemic medications: eight were treated with cyclosporine, although two of them still did not respond. Dapsone was tried in five patients; one of whom had a satisfactory response, while three patients had a fair response. Seven patients were treated with an additional systemic corticosteroid; three of whom had a good response and two patients still had unremarkable response.

Table 2 Patients' characteristics between sexes

	Male	Female
Age at first hospital visit (year)	22.1 ± 5.4	25.2 ± 8.6
Duration (month)	30.8 ± 29.2	25.2 ± 18.7
Age of onset (year)		
10–19	124 (66)	7 (47)
20–29	52 (28)	4 (27)
30–39	9 (5)	3 (20)
40–49	3 (2)	1 (7)
Absence of visible skin eruption	27 (14)	2 (15)
Co-morbidities		
Atopic dermatitis	10 (5)	6 (40)
Allergic rhinitis	3 (2)	0 (0)
Asthma	2 (1)	0 (0)
Crohn's disease	2 (1)	1 (7)
Dermographism	7 (4)	0 (0)
Others [†]	4 (2)	0 (0)
Relation with perspiration	15 (8)	0 (0)
Responsiveness to antihistamine treatment		
Poor	45 (24)	1 (7)
Fair	71 (38)	6 (40)
Good	72 (38)	8 (55)
House dust mite allergy in MAST	12 (7)	2 (15)

[†]n: penicillin allergy 1, Graves disease 1, Seizure 2. Values are presented as mean ± standard deviation (range) or number (%). MAST, multiple allergen simultaneous test.

Table 3 Patient characteristics between groups with or without skin eruption

	With skin lesion	Without skin lesion
Age at first hospital visit (year)	22.3 ± 5.8	22.4 ± 5.5
Duration (month)	30.7 ± 28.4	28.5 ± 30.3
Age of onset (year)		
10–19	114 (66)	17 (59)
20–29	47 (27)	9 (31)
30–39	9 (5)	3 (10)
40–49	4 (2)	0 (0)
Distribution of sex		
Male	161 (93)	27 (93)
Female	13 (8)	2 (7)
Co-morbidities		
Atopic dermatitis	14 (8)	2 (7)
Allergic rhinitis	3 (2)	0 (0)
Asthma	1 (1)	1 (3)
Crohn's disease	2 (1)	1 (3)
Dermographism	6 (3)	1 (3)
Others [†]	4 (2)	0 (0)
Relation with perspiration	12 (7)	3 (10)
Responsiveness to antihistamine treatment		
Poor	32 (18)	14 (48)
Fair	68 (39)	9 (31)
Good	74 (43)	6 (21)
House dust mite allergy in MAST	12 (7)	2 (7)

[†]n: penicillin allergy 1, Graves disease 1, Seizure 2. Values are presented as mean ± standard deviation (range) or number (%). MAST, multiple allergen simultaneous test.

Comorbidity

A total of 20 patients (10%) had comorbid atopic diseases, some of which were concurrent; namely, atopic dermatitis

(AD) (16 patients), allergic rhinitis (four patients) and asthma (two patients). One of the AD patients also had concomitant allergic rhinitis and asthma. One patient had only asthma. The prevalence of AD was significantly higher in female patients than male patients ($P < 0.01$), although there was no statistically significant difference in this comorbidity according to the presence of skin eruption. In addition, seven patients (4%) had accompanying dermographism and one patient had concurrent cold urticaria proven by an ice-cube test. One patient had a penicillin allergy and two patients had a history of seizures and antiepileptic medication. Interestingly, three patients had accompanying Crohn's disease, although the ChU symptoms did not correspond with the severity of Crohn's disease symptoms. A 31-year-old male patient had concurrent Graves' disease with positive thyroglobulin antibody and anti-thyroid peroxidase antibody tests. His urticaria symptoms paralleled those in Graves' disease: as the Graves' disease was controlled and thyroid function tests normalised, the urticaria became tolerable. Another patient also had a positive thyroglobulin antibody test, but other laboratory evaluations of the thyroid were unrevealing.

Relation to perspiration

Altogether 15 patients (7%) claimed that their urticaria was worse with hypohidrosis (i.e., the symptoms were aggravated when sweating was impaired even when they were hot). Furthermore, they felt that the urticaria improved once sweating was initiated. All of these were male, and three (11%) had no visible skin eruption.

Laboratory abnormalities

Three patients (2%) showed anti-nuclear antibody (ANA) positivity. However, ANA-positive patients did not have any specific distinguishing features. Although 14 (7%) patients were positive for a house dust mite allergy in the MAST assay, there was not a statistically significant difference in the number of patients according to their sex or the presence of skin eruption. Of these patients, two had multiple positive results for more than 10 items in the MAST assay, including citrus mix, peach, rice, barley and cockroach. These patients had a longer duration of the disease (between 7 and 10 years), and the symptoms were more difficult to control with antihistamine therapy.

Male predominance, particularly in the young adult group

In Korea, military service is obligatory; most men are enlisted in their late teens and early twenties. This period overlaps with the age of the highest prevalence of ChU. To evaluate the effect of medical documentation for military service on the marked male prevalence of ChU in Korea, we separated the young adult group (19–29-year olds) into two age groups: 19–23-year olds, which is the usual age of military enlistment, and 24–29-year olds. Among 148 young adult patients, 141 (95%) were male (Table 4). Of males,



Figure 1 Morphology of skin eruption showing (a) pinhead-sized papular wheal with surrounding erythematous halo (white arrow: papular wheal, black arrow: surrounding halo); (b) flesh-coloured follicular wheal-like eruption; (c) erythematous patch without wheal; (d) no skin eruption after provocation with exercise.

Table 4 Male predominance is pronounced, particularly in the young adult group

	Age 19–23	Age 24–29	Total
Male, <i>n</i>	111	30	141
% of gender group	78.7	21.3	100
% of age group	97.4	88.2	95.3
Female, <i>n</i>	3	4	7
% of gender group	42.9	57.1	100
% of age group	2.6	11.8	4.7
Total, <i>n</i>	114	34	148
% of gender group	77.0	25.0	100

the 19–23-year age group accounted for 111 patients (79%), while the 24–29-year age group accounted for 30 patients (21%). Conversely, of the seven female patients, three (43%) were between the ages of 19 and 23. Male predominance in the 19–23-year age group was statistically significant ($P < 0.05$). In the remaining 55 patients not included in the young adult group, 47 (86%) were male and eight (15%) were female. These results revealed an overall male predominance for ChU that was more noticeable in the young adult age group, particularly in the 19–23-year age group.

DISCUSSION

ChU is known to be prevalent in young adults. In a German study of 493 participants, the overall prevalence of ChU was 11%, with the highest prevalence in the 26–28-year age group.³ Prevalence is much lower in countries with hot and humid weather. The overall prevalence of

ChU was reported as 4% (25 out of 600 students) in India, and six of 86 physical urticaria patients had ChU in Thailand.^{4,5} In a recent Korean study, ChU was most prevalent among patients in their twenties (61%), and most patients developed their symptoms during their teens (51%).⁶ Our study demonstrated similar patterns: the highest prevalence was recorded among patients in their twenties (56%), with the onset being most common in the second decade of life (65%). The cause of ChU prominence in young adults still needs to be elucidated.

Regarding sex distribution, there have been contradictory reports. Whereas one study noted a male predominance, others have found that both sexes are affected equally.^{5,4,7} Kim and colleagues⁶ noted that the striking male predominance in the Korean population is readily apparent in the medical documentation of young male adults for their mandatory military service. In our analysis, ChU prevalence was skewed towards male sex, more notably in the young adult group, and this effect was even more conspicuous in the 19–23-year age group, which is consistent with the age of military enlistment. Thus, the sex skewing may be ascribed to a higher detection rate, not a higher incidence of ChU among young men in Korea.

In 15 patients, ChU was complicated by hypohidrosis. The sweat glands express muscarinic acetylcholine receptors and an intracutaneous injection of cholinergic agents produced a wheal with satellite lesions in approximately one-third of patients.^{7–9} In addition, poral occlusion that interferes with sweat secretion has been thought to result in sweat leakage, which might contain numerous enzymes and cytokines, inducing local inflammation and wheals.¹⁰

Exacerbation of ChU in the winter suggests that sweating in the summer may prevent the formation of keratotic plugs and occlusion. Immediate type hypersensitivity to unknown substances in sweat has also been suggested in light of positive reactions induced by an intradermal injection of a patient's own diluted sweat.^{11,12} Anti-immunoglobulin E therapy with omalizumab has been found to be effective in this population.¹⁵ In our study, one patient with accompanying anhidrosis showed a post-ganglionic cholinergic deficit and another, who cited symptom aggravation with reduced sweating, showed moderate improvement when treated with 12% ammonium lactate lotion.

Hypersensitivity to autologous sweat is also considered to be responsible for concurrent atopic diseases, including AD. Recently, MGL₁₃₀₄, an antigen secreted by the fungus *Malassezia globosa* in human sweat, has been implicated in both AD and ChU.¹⁴ Given that most ChU patients have mild symptoms and do not seek medical help, ChU might be identified in AD patients already seeking medical treatment.⁵ Also, ChU may be misdiagnosed in AD patients complaining of stinging and pruritus exacerbated by hot weather, leading to an overestimation of accompanying atopic diseases.⁶ Seven patients (4%) had concurrent dermatographism and one patient had cold urticaria, consistent with previous reports on frequently accompanying physical urticarias.^{6,15,16} Other comorbidities included Crohn's disease, penicillin allergy and positive autoantibodies like ANA. Although they are only a small fraction of the study population, accompanying autoimmune diseases or autoantibodies in patients suggest a role for autoimmunity in ChU pathogenesis.

Although oral antihistamines are a primary treatment for ChU, some patients do not respond successfully to antihistamine therapy.^{17–19} In this study, most patients showed at least partial improvement with oral antihistamines. However, 23% of them had a poor response and required adjunctive or alternative treatments, including cyclosporine, dapsone or corticosteroids. Some patients were still not responsive to secondary treatments.

Interestingly, 29 out of 203 patients complained of a severe burning sensation and pruritus after exercise or passive warming without visible skin eruption. They did not have a distinctive sex bias, distribution of onset age, or comorbidities. The only difference was their responsiveness to antihistamine therapy: they exhibited a significantly poorer response than patients with a visual urticarial eruption. Another 12 patients had only non-oedematous erythematous macules without wheals.

Intense pruritus and burning induced by heat, exercise, hot food or emotion, which was relieved by cooling, was once termed cholinergic pruritus.^{20,21} When exercise and warmth-induced pruritus was accompanied solely by a macular punctuate or generalized erythema, it was called cholinergic erythema.²² These conditions were regarded as variants of ChU. Benzoyl scopolamine, which blocks cholinergic receptors in the skin, has been shown to prevent exercise-induced cholinergic erythema. Cholinesterase levels are lower in the skin of patients with cholinergic pruritus and with ChU than in healthy controls.^{23,24} These data

indicate that these three conditions might represent a spectrum of the same disorder.

Our study had several limitations. First, because the study was a retrospective review, a thorough investigation of the role of perspiration and distinguishing between follicular and non-follicular wheals was not possible. Second, some young male patients were lost for follow up to undertake mandatory military service, which might lead to biases in the disease duration and response to treatment.

Despite these limitations, this study is one of the largest studies involving more than 200 ChU patients, with the inclusion of cholinergic pruritus and cholinergic erythema as minor variants of ChU. Since its first description in 1942, the pathomechanism of ChU has remained poorly understood and many ChU symptoms overlap with those associated with other physical urticarias. By including cholinergic pruritus and erythema in the spectrum of ChU, we found the clinical manifestations and pathomechanisms of ChU were more wide-ranging and heterogeneous than previously suspected. Therefore, further studies on both pathogenesis and treatments are necessary to reinforce treatment strategies against ChU. In addition, physicians should be aware of the comprehensive scope of ChU in order to provide ChU patients with appropriate treatment and to improve their quality of life.

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