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Recurrent chronic spontaneous urticaria in a tropical country: Clinical characteristics and associated factors

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Abstract

Background: Limited data exist regarding recurrent chronic spontaneous urticaria (RCSU) following complete disease remission.

Objective: This study investigated the clinical characteristics and factors associated with RCSU.

Methods: We retrospectively reviewed data from chronic spontaneous urticaria (CSU) patients who actively visited the Urticaria Center of Reference and Excellence, Siriraj Hospital, between January 2021 and December 2023. Medical records were analyzed through May 2024. The RCSU was defined as a new CSU episode occurring after a 6-month symptom-free period without treatment.

Results: Among 179 CSU patients, 19 (10.6%) developed RCSU. These patients had a mean age of 40 (SD 14.9) years, with a female predominance. The mean time to RCSU recurrence was 1.96 (SD 2.05) years. The UAS7 and medication scores were not significantly different between the recurrence and nonrecurrence groups (P = 0.675, P = 0.77). Multivariate analysis revealed that a shorter disease remission time from the first episode onset (< 3 years) was significantly associated with RCSU (odds ratio 5.13, 95%CI 1.83–14.29; P = 0.002).

Conclusion: The RCSU rate was 10.6%. The time to disease remission from the first episode onset significantly associated with RCSU. Several clinical characteristics may corelate with the recurrence: younger age at onset, the presence of angioedema, chronic inducible urticaria comorbidity, systemic corticosteroid use, and positive antinuclear antibody status.

Key words: Chronic spontaneous urticaria, Recurrent chronic spontaneous urticaria, shorter disease remission of chronic urticaria, clinical characteristics of recurrent chronic spontaneous urticaria, associated factors of recurrent chronic spontaneous urticaria

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Introduction

Chronic spontaneous urticaria (CSU) manifests as wheals and/or angioedema persisting for at least 6 weeks.[1] CSU affects approximately 0.1% of the population.[2,3] Disease duration typically ranges from 2 to 5 years, although some patients experience symptoms beyond 20 years.[2,4,5]

Approximately 70% of patients without identifiable precipitating factors maintain active disease after 1 year.[6,7] Previous research has identified several factors associated with prolonged disease duration, including disease severity, the presence of angioedema, and chronic inducible urticaria (CIndU) coexistence.[5-8] Additional factors include the presence of antithyroid antibodies, a positive autologous serum skin test, multiple CSU episodes, and late-onset disease occurring after age 45.[5-8]

Conversely, certain factors correlate with disease improvement. These include brief symptom duration before the initial visit, childhood onset, and H_1 antihistamine monotherapy.[9]

Some patients develop recurrent chronic spontaneous urticaria (RCSU) after achieving complete remission. Studies report RCSU rates of 13%–21% among CSU patients.[10-12] Limited research exists regarding the clinical characteristics and associated factors of RCSU, particularly in Thailand which is located in tropical regions. Tropical regions are the area which located between the Tropic of Cancer and the Tropic of Capricorn. Tropical countries include Thailand, the Philippines, Malaysia, Singapore, Indonesia, southern India etc. The climate in most of these countries located in tropical regions are high temperatures and humidity.[13] A study mentioned that the temperature may affect the risk of urticaria.[14] However, the relationship between temperature and RCSU has not been investigated yet. Most studies originate from higher-latitude countries with different climatic conditions.

Previous research in nontropical regions has indicated that combination treatments, asthma comorbidity, and autoimmunity are correlated with RCSU.[10,11] However, data from tropical countries remain scarce. This study aimed to investigate the clinical characteristics and associated factors of RCSU in a tropical setting.

Methods

Study design and population

This retrospective cohort study examined patients with CSU who actively attended the Urticaria Center of Reference and Excellence at Siriraj Hospital's Department of Dermatology. The study period spanned from January 2021 through December 2023, with medical record review continuing through May 2024. The Siriraj Institutional Review Board approved this study (approval number 422/2024).

Case definition and exclusion criteria

We defined RCSU as a new CSU episode occurring after at least 6 months without symptoms and cessation of effective treatment.[15] The study excluded patients with urticarial vasculitis, unclear diagnoses, pure CIndU, or concomitant skin diseases.

Data collection and disease severity assessment

The data collected encompassed demographics, disease severity, clinical course, treatments, disease resolution, laboratory investigations, and recurrence patterns. Disease severity assessment utilized a UAS7 scores and a medication scoring system. The UAS7 scores are calculated from the sum total of daily wheal (range 0-3) and the intensity of pruritus (range 0-3) for 7 consecutive days. The UAS7 severity scores are classified as severe urticaria (28–42 points), moderate urticaria (16–27 points), and mild urticaria (0–15 points).[16] The scoring system assigned weighted points for various medications: oral antihistamines (2 points for regular dose, 8 points for fourfold dose), systemic corticosteroids (< 11 mg, 5 points; 11–25 mg, 10 points; > 25 mg, 15 points), ciclosporin (8 points for > 3 mg/kg/day), hydroxychloroquine (6 points), and leukotriene receptor antagonists (2 points).[17,18]

Comparative analysis

We conducted additional analyses to compare factors between two groups: patients who achieved complete cure without recurrence by the end of the study, and those who experienced RCSU.

Statistical analysis

Data analysis was performed with PASW Statistics, version 18 (SPSS Inc, Chicago, IL, USA). We present descriptive statistics as frequencies, percentages, means, standard deviations, or medians with ranges. Chi-square or Fisher's exact tests were used to evaluate associations between categorical variables as appropriate.

Simple binary logistic regression identified factors associated with CSU recurrence. Variables yielding *P* values less than 0.20 in univariate analysis and factors of specific interest were subjected to multiple logistic regression analysis. Statistical significance was set at $P < 0.05$.

Results

Among the 179 CSU patients, 19 (10.6%) developed RCSU. The mean time to RCSU recurrence was 1.96 years (SD 2.05). The RCSU patients had a mean age of 40.6 years (SD 14.9), with a female predominance (78.9%). The first episode duration in RCSU patients ranged from 0.5 to 9 years, with a mean of 2.3 years. The maximum recurrences episode in this study were 2 episodes.

Allergic rhinitis emerged as the most common atopic comorbidity (27.9%), followed by atopic dermatitis (19.7%) and asthma (5%). Disease severity evaluation revealed mean (SD) of UAS7 scores of 19.2 (11.2) and a median medication score of 8 (range 19). Five patients (26.3%) in the recurrent group had concurrent CIndU: two with symptomatic dermographism, one with cold urticaria, one with delayed pressure urticaria, and one with cholinergic urticaria. Among the RCSU patients, 16 (84.2%) experienced one episode of recurrence, whereas three (15.8%) experienced two episodes. The clinical characteristics of the patients are detailed in **Table 1**.

Factors associated with recurrence

The factors associated with the recurrence of CSU are shown in **Table 2**. Patients with CSU recurrence tended to have a younger age at onset during their first episode. The sex distribution was not significantly different between the groups, maintaining a female predominance. Angioedema and CIndU occurred more frequently in the recurrence group. A shorter disease remission time from the first episode onset (< 3 years) was significantly correlated with RCSU (odds ratio [OR] 4.81, 95% confidence interval CI 1.78–12.99; $P = 0.002$).

Table 1. Clinical and demographic characteristics of patients with chronic spontaneous urticaria: comparison of recurrence and non-recurrence groups.

Clinical characteristics	Total N (%) N = 179	Non-recurrence N (%) N = 160	Recurrence N (%) N = 19		
			Total N = 19	1 episode N = 16	2 episodes N = 3
Age of onset, years, mean (SD)	40.6 (15.5)	40.7 (15.6)	40 (14.9)	38.1 (14.6)	50.3 (14.2)
Sex					
Male	42 (23.5)	39 (23.8)	4 (21.1)	3 (18.8)	1 (33.3)
Female	137 (76.5)	125 (76.2)	15 (78.9)	13 (81.2)	2 (66.7)
Time of the first episode, years, median (range)	4.3 (25.1)	4.9 (25.1)	2.3 (8.5)	2.2 (8.5)	2.9 (1.9)
Comorbidity					
Thyroid disease	15 (8.4)	13 (8.1)	2 (10.5)	2 (12.5)	0
Hypertension	33 (18.4)	29 (18.1)	4 (21.1)	3 (18.8)	1 (33.3)
Dyslipidemia	39 (21.8)	35 (21.9)	4 (21.1)	4 (25)	0
Diabetes mellitus	12 (6.7)	9 (5.6)	3 (15.8)	3 (18.8)	0
Personal history of atopy					
Asthma	9 (5)	6 (3.8)	3 (15.8)	3 (18.8)	0
Allergic rhinitis	50 (27.9)	44 (27.5)	6 (31.6)	5 (31.3)	1 (33.3)
Atopic dermatitis	35 (19.7)	31 (19.5)	4 (21.1)	4 (25)	0
Family history of atopy	65 (36.3)	60 (36.8)	7 (36.8)	6 (37.5)	1 (33.3)
Disease severity					
UAS7 scores, mean (SD)	19.2 (11.2)	19.3 (10.9)	18.5 (12.9)	18.3 (13.1)	19.7 (15)
Medication scores, median (range)	8 (35)	8 (35)	8 (19)	8 (16)	18 (19)
Type of chronic spontaneous urticaria					
CSU	146 (81.6)	132 (82.5)	14 (73.7)	11 (68.8)	3 (100)
CSU with CIndU	32 (17.9)	28 (17.5)	5 (26.3)	5 (31.2)	0 (20)

Abbreviations: CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; SD, standard deviation; UAS7, weekly urticaria activity score

Table 2 Univariate and multivariate analysis of factors associated with chronic spontaneous urticaria recurrence.

	Non-recurrence N = 160	Recurrence N = 19	Univariate analysis		Multivariate analysis	
			Odds ratio (95%CI)	*P* value	Odds ratio (95%CI)	*P* value
Age of onset, years						
< 40	88 (55)	11 (57.9)	1.12 (0.43-2.94)	0.810	0.79 (0.28-2.23)	0.655
≥ 40	72 (45)	8 (42.1)	1		1	
Sex (N, %)						
Male	38 (23.8)	4 (21.1)	1		1	
Female	122 (76.2)	15 (78.9)	1.17 (0.37-3.73)	0.793	1.34 (0.39-4.56)	0.638
Symptoms (N, %)						
Urticaria	110 (68.8)	12 (63.2)	1			
Urticaria and angioedema	50 (31.2)	7 (36.8)	1.30 (0.48-3.46)	0.621		

Table 2 Univariate and multivariate analysis of factors associated with chronic spontaneous urticaria recurrence.

	Non-recurrence N = 160	Recurrence N = 19	Univariate analysis		Multivariate analysis	
			Odds ratio (95%CI)	*P* value	Odds ratio (95%CI)	*P* value
Type of chronic urticaria						
CSU	132 (83.1)	14 (73.7)	1			
CSU with CIndU	27 (16.9)	5 (26.3)	1.33 (0.77-2.30)	0.315		
Time of disease remission since onset of the first episode, years						
< 3	42 (26.3)	12 (63.2)	4.81 (1.78-12.99)	0.002	5.13 (1.83-14.29)	0.002
≥ 3	118 (73.8)	7 (36.8)	1		1	
Disease severity assessment						
UAS7 scores						
≤ 16	74 (46.3)	10 (52.6)	1.29 (0.49-3.34)	0.599		
> 16	86 (53.7)	9 (47.4)				
Medication score						
< 8	48 (30)	6 (31.6)	1.07 (0.39-3)	0.887		
≥ 8	112 (70)	13 (68.4)				
Medications (N, %)						
Up-dose (4-fold) second generation H_1 antihistamines	107 (66.9)	11 (57.9)	0.68 (0.26-1.79)	0.437		
H_1 antihistamines alone	93 (58.1)	10 (52.6)	0.80 (0.31-2.08)	0.647		
H_1 antihistamines plus leukotriene receptor antagonist	3 (1.9)	1 (5.3)	NA			
H_1 antihistamines plus prednisolone	38 (23.8)	7 (36.8)	1.87 (0.69-5.10)	0.219		
H_1 antihistamines plus prednisolone and ciclosporin	2 (1.3)	1 (5.3)	NA			
H_1 antihistamines plus prednisolone and omalizumab	13 (8.1)	0	NA			
H_1 antihistamines plus prednisolone and ciclosporin and omalizumab	11 (6.9)	0	NA			
Laboratory investigations						
Elevation of eosinophil	11 (6.9)	2 (10.5)	1.59 (0.33-7.80)	0.562		
Elevation of ESR	26 (28.6)	3 (33.3)	1.25 (0.29-5.38)	0.764		
Positive ANA	23 (20.4)	6 (42.9)	2.94 (0.93-9.30)	0.067		
Presence of anti-thyroid antibody	15 (16.3)	2 (28.6)	2.05 (0.36-11.59)	0.415		
Higher level of IgE	30 (52.6)	1 (33.3)	NA	0.524		

Abbreviations: ANA, antinuclear antibody; CI, confidence interval; CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; ESR, erythrocyte sedimentation rate; IgE, immunoglobulin E; UAS7, weekly urticaria activity score

Table 3 Clinical characteristics comparison between cured and recurrent chronic spontaneous urticaria patients.

	Cure N = 19	Recurrence N = 19	*P* value
Age of onset, years			NA
< 40	8 (42.1)	8 (42.1)	
≥ 40	11 (57.9)	11 (57.9)	
Sex (N, %)			0.703
Male	5 (26.3)	4 (21.1)	
Female	14 (73.7)	15 (78.9)	
Type of lesion (N, %)			NA
Urticaria	12 (63.2)	12 (63.2)	
Urticaria and angioedema	7 (36.8)	7 (36.8)	
Type of chronic urticaria			0.209
CSU	17 (89.5)	14 (73.7)	
CSU with CIndU	2 (10.5)	5 (26.3)	
Time of disease remission since onset of the first episode, years			0.515
< 3 years	9 (47.4)	12 (63.2)	
≥ 3 years	10 (52.6)	7 (36.8)	
Disease severity assessement			
UAS7 scores			0.746
≤ 16	9 (47.4)	10 (52.6)	
> 16	10 (52.6)	9 (47.4)	
Medication score			0.732
< 8	7 (36.8)	6 (31.6)	
≥ 8	12 (63.2)	13 (68.4)	
Medications (N, %)			
H_1 antihistamines alone	9 (47.4)	10 (52.6)	0.746
Up-dose (4-fold) second generation H_1 antihistamines	12 (63.2)	11 (57.9)	0.740
H_1 antihistamines plus leukotriene receptor antagonist	1 (5.3)	1 (5.3)	NA
H_1 antihistamines plus prednisolone	6 (31.6)	7 (36.8)	0.732
H_1 antihistamines plus prednisolone and ciclosporin	1 (5.3)	1 (5.3)	NA
H_1 antihistamines plus prednisolone and omalizumab	2 (10.5)	0	NA
H_1 antihistamines plus prednisolone and ciclosporin and omalizumab	0	0	NA

Abbreviations: CI, confidence interval; CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; UAS7, weekly urticaria activity score

Treatment patterns and laboratory findings

UAS7 scores between the groups revealed no statistical different. (P = 0.675) Medication scores were similar between the groups, with a median of 8 in both the recurrence group (range 2-21) and the non-recurrence group (range 2-37; P = 0.77). All patients received H_1 antihistamines. The recurrence group had slightly lower rate in treated with 4-fold H_1 antihistamines. (57.9% vs 66.9%, OR 0.68, 95%CI (0.26-1.79); P = 0.437) The recurrence group had higher rates of combination therapy with H_1 antihistamines plus prednisolone than nonrecurrent patients did (36.8% vs 23.8%, OR 1.87, 95%CI 0.69-5.10; P = 0.219).

Laboratory parameters were not significantly different between the groups in terms of eosinophil elevation, the erythrocyte sedimentation rate, antinuclear antibody positivity, or the presence of antithyroid antibodies. Patients with positive antinuclear antibody tended to have higher rate of recurrence. (OR 2.94, 95%CI (0.93-9.30); P = 0.067)

Multivariate analysis

Multivariate analysis confirmed that a shorter disease remission time from the first episode onset was significantly associated with recurrence (OR 5.13, 95%CI 1.83-14.29; P = 0.002). The subgroup comparison between completely cured patients and RCSU patients revealed no significant differences in age at onset, sex, angioedema, CIndU comorbidity, disease duration, or treatments (**Table 3**).

Discussion

CSU represents a common skin disorder affecting the general population. Approximately 70% of CSU patients maintain symptoms beyond 1 year from initial onset.[5-7,9,19] Several factors relate with extended disease duration, including the presence of angioedema, increased disease severity (particularly urticaria activity scores > 28), symptom duration exceeding 6 months before treatment initiation, older age at onset, and multiple combination therapies.[6,9,19-21] However, some studies have reported no correlation between the presence of angioedema and disease duration.[9,22]

The medical community has not yet established a standardized definition for RCSU, particularly regarding the required symptom-free interval before new episode onset. However, the World Allergy Organization Urticaria Committee states that the definition of CSU remission is to achieve complete disappearance of urticaria symptoms and signs in the absence of any treatment for at least 6 months.[23] Kim et al proposed defining RCSU as a new CSU occurrence following complete symptom resolution for at least 6 months without effective treatment.[10] Therefore, we are in agreement with this definition. In addition, this definition will benefit the medical practice and clinicians to have long-term follow up in CSU patients in ordinary hospital. Previous studies reported RCSU rates ranging from 13%-21% in adults and 17.1% in children (**Table 4**).[8,10,11,24,25] Our study found a lower RCSU rate of 10.6%, possibly due to the limited

Table 4. Published studies on recurrent chronic spontaneous urticaria: a literature review (2018–2024)

Study (year)	Country	Study population (total N)	Recurrence rate	Factors associated with RCSU
Curto-Barredo et al (2018)[8]	Spain	Patients aged over 16 years diagnosed with CSU (549)	- 20.0%: > 1 episode - 5.8%: > 2 episodes	CSU without CIndU
Kim et al (2018)[10]	The United States of America	Patients aged over 17 years diagnosed with CSU (292)	39/292 (13.4%)	Combination treatments with anti-inflammatory agents, immunosuppressant and omalizumab
Curto-Barredo et al (2019)[21]	Spain	Patients aged over 16 years diagnosed with CSU (549)	105/548 (19.2%)	- Absence coexisting of psychiatric diseases - Shorter disease duration - Absence of CIndU - Stress triggering factor - Lower levels of basophils, eosinophils, alkaline phosphatase and total IgE
Özyılmaz-Bozat et al (2020)[20]	Turkey	Children who were diagnosed with CSU (76) (age not mentioned; clinical communication)	13/76 (17.1%)	- Higher age at symptom onset (≥ 10 years) - Presence of anti-thyroid antibodies
Toubi and Vadasz (2021)[11]	Israel	Patients aged 18-70 years diagnosed with CSU (180)	25/119 (21%)	- Existing of bronchial asthma - Increased levels of total IgE - Presence of anti-thyroid peroxidase antibodies - Duration of first episode > 3 years
Our study (2024)	Thailand	Patients aged over 18 years diagnosed with CSU (183)	19/179 (10.6%)	- Time of disease remission since onset of the first episode < 3 years - Age onset < 40 years old - Angioedema - Concomitant with CindU - Positive ANA - Treatment combination with prednisolone

Abbreviations: ANA, antinuclear antibody; CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; IgE, immunoglobulin E; RCSU, recurrent chronic spontaneous urticaria; RR, relative risk

number of patients. Temperature may influence urticaria patterns. Studies from China and Singapore demonstrated a lower acute urticaria risk and incidence during high ambient temperature periods.[26,27] Additional research is needed to determine whether higher ambient temperatures influence RCSU rates.

The maximum recurrence in our study were 2 episodes. CSU is a disease of long duration, and according to a study by Kulthanan et al., the average duration in Thai patients is 1.07 years, with only 35% of patients achieving remission within one year.[7] Patients with CSU may have a chance of recurrence, but it is unlikely to be multiple recurrences. The study of Barredo et al reported that only 5.8% of the patients had more than 2 episodes.[8]

Factors associated with RCSU

Clinical characteristics and risk factors

Our findings suggest an increased likelihood of RCSU in patients with a younger onset age (< 40 years) and angioedema, although these associations did not reach statistical significance. A Spanish study of 549 CSU patients similarly reported higher angioedema rates in the recurrence group without statistical significance (21% vs 15%, $P = 0.145$).[25] While Curto-Barredo et al associated CIndU absence with RCSU, our results showed contrary findings.[8,25]

Time to disease remission from the first episode onset

Our study identified that a shorter initial disease remission time was significantly correlated with recurrence. Patients who achieved remission within 3 years of onset presented fivefold greater odds of recurrence, which aligns with the findings of Curto-Barredo et al.[25] We hypothesize that rapid initial remission may represent temporary symptom resolution rather than true disease resolution. Conversely, Toubi and Vadasz reported higher recurrence rates in patients whose initial CSU duration exceeded 3 years.[11] Their study population, which comprised antihistamine-refractory patients requiring systemic steroids, may represent more severe disease cases.

Disease severity and treatment

Disease severity assessment using both UAS7 and medication scores was not significantly different between the RCSU and non-RCSU groups. However, patients receiving a combination of antihistamines and immunosuppressive therapy were more likely to have RCSU, suggesting greater disease severity in recurrent cases. Kim et al reported a doubled relative risk of RCSU in patients using immunosuppressants, anti-inflammatory agents, or omalizumab. Treatment beyond H_1 antihistamines or systemic steroids is associated with approximately 20% higher recurrence rates.[10] Using different second-generation H_1 antihistamines may not affect the prognosis of CSU. The structure of second-generation H_1 antihistamines may differ from each other, but they all share the same mechanism of action. According to the guideline, second-generation H_1 antihistamines are used as symptomatic pharmacological treatment. However, to our best knowledge, there is lack of clinical trials comparing the efficacy of all second-generation H_1-antihistamines in the treatment of urticaria.[1]

Laboratory parameters

Our study revealed no statistically significant differences in laboratory parameters between the groups, although antinuclear antibody positivity tended to be greater in recurrent cases. Previous research associated increased total immunoglobulin E levels and antithyroid peroxidase positivity with recurrence.[11,24] Autoimmune antibodies may destabilize mast cells, potentially increasing the risk of future recurrence.[11] However, Spanish research found significantly lower basophil, eosinophil, alkaline phosphatase, and total immunoglobulin E levels in recurrent CSU patients.[25]

Study limitations

Our study faced some limitations. The retrospective design may have resulted in incomplete documentation. The short observation period might have led to an underestimation of RCSU rates, as some patients in the nonrecurrence group may not yet have achieved disease resolution. Our small RCSU patient cohort, which was limited to those with complete first-episode records at our clinic, may underrepresent true recurrence rates.

Conclusion

This study found a 10.6% RCSU rate following initial episode remission. A shorter disease remission time from the first episode onset (< 3 years) significantly associated with RCSU. Additional factors suggesting increased recurrence risk include younger onset age (< 40 years), the presence of angioedema, CIndU comorbidity, and systemic steroid therapy. Future long-term follow-up studies may provide additional insights. We recommend developing consensus guidelines for RCSU definitions and symptom-free interval requirements.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

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