International Journal of Dermatology

WILEY

ORIGINAL ARTICLE

Dysmenorrhea in Chronic Spontaneous Urticaria: A Subset of Patients Report Worsening and Partial Antihistamine Benefit: UCARE HURDLE-I Study

Murat Türk[1] | Muhammed Burak Yücel[2,3] | İnsu Yılmaz[1] | Ragıp Ertaş[3] | Ümit Murat Şahiner[4] | Semra Demir[5] | Aslı Gelincik[5] | Derya Ünal[5] | Şule Çelik Kamacı[5] | Merve Hörmet İğde[5] | Pelin Korkmaz[5] | Zafer Türkoğlu[6] | Nazlı Caf[6] | Özge Sevil Karstarlı[7] | Sevda Edis Çınar[8] | Elif Açar[1] | Elif Aktaş Yapıcı[1] | Hatice Eylül Bozkurt Yılmaz[1] | Serpil Köylüce[1] | Özlem Su Küçük[9] | Melisa Özay[9] | Arzu Dilşat Zengin[9] | Neslihan Demirel Öğüt[10] | Simge Ünal[10] | Deniz Özçeker[11] | Güler Yıldırım[11] | Aytül Zerrin Sin[12] | Kasım Okan[12] | Ragıp Fatih Kural[12] | Ebru Damadoğlu[13] | Hazal Kayıkçı[13] | Sevim Bavbek[14] | Erman Gıdık[14] | Esen Özkaya[15] | Yasemin Erdem[15] | Bülent Enis Şekerel[4] | Özge Uysal Soyer[4] | Nadira Nabiyeva Çevik[4] | Öner Özdemir[16] | Ece Tüsüz Önata[16] | Ümmügülsüm Dikici[16] | Murat Borlu[17] | Eda Öksüm Solak[17] | Esra Adışen[18] | Mehmet Gülengül[18] | Rabia Öztaş Kara[19] | Mustafa Tosun[20] | Raif Coşkun[21] | Marcus Maurer[22,23,†] | Torsten Zuberbier[22,23] | Emek Kocatürk[22,23,24]

[1]Division of Allergy and Clinical Immunology, Erciyes University School of Medicine, Kayseri, Türkiye | [2]Department of Dermatology, Ergani State Hospital, Diyarbakır, Türkiye | [3]Department of Dermatology, Kayseri Faculty of Medicine, University of Health Sciences, Kayseri City Education and Research Hospital, Kayseri, Türkiye | [4]Department of Pediatric Allergy, Hacettepe University School of Medicine, Ankara, Türkiye | [5]Division of Immunology and Allergy Diseases, Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Türkiye | [6]Department of Dermatology and Venereology, Başakşehir Çam ve Sakura City Hospital, Health Sciences University, School of Medicine, Istanbul, Türkiye | [7]Department of Dermatology, Pamukkale University, Denizli, Türkiye | [8]Department of Dermatology, Servergazi State Hospital, Denizli, Türkiye | [9]Department of Dermatology and Venereology, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Türkiye | [10]Department of Dermatology and Venereology, Uşak University Faculty of Medicine, Uşak, Türkiye | [11]Department of Pediatric Allergy and Immunology, Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Türkiye | [12]Division of Allergy and Clinical Immunology, Department of Internal Medicine, Ege University Medical Faculty, Izmir, Türkiye | [13]Division of Allergy and Clinical Immunology, Department of Chest Diseases, Hacettepe University School of Medicine, Ankara, Türkiye | [14]Division of Immunology and Allergic Diseases, Department of Chest Diseases, Ankara University School of Medicine, Ankara, Türkiye | [15]Department of Dermatology and Venereology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Türkiye | [16]Division of Allergy and Immunology, Department of Pediatrics, Sakarya Research and Training Hospital, Faculty of Medicine, Sakarya University, Sakarya, Türkiye | [17]Department of Dermatology and Venereology, Faculty of Medicine, Erciyes University School of Medicine, Kayseri, Türkiye | [18]Department of Dermatology, Gazi University Faculty of Medicine, Ankara, Türkiye | [19]Department of Dermatology, Sakarya University Faculty of Medicine, Sakarya, Türkiye | [20]Department of Dermatology, Sivas Cumhuriyet University Faculty of Medicine, Sivas, Türkiye | [21]Division of Allergy and Immunology, Cemil Tascioglu City Hospital, Istanbul, Türkiye | [22]Institute of Allergology, Charité – Universitätsmedizin Berlin, Berlin, Germany | [23]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany | [24]Department of Dermatology, Bahçeşehir University School of Medicine, Istanbul, Türkiye

Correspondence: Murat Türk (muratturk@erciyes.edu.tr)

Received: 26 August 2025 | **Revised:** 16 December 2025 | **Accepted:** 18 December 2025

Keywords: chronic spontaneous urticaria | dysmenorrhea | histamine | skin prick test

ABSTRACT

Background: Histamine plays a central role in CSU pathogenesis and may contribute to extracutaneous symptoms such as dysmenorrhea, but this relationship has not been fully examined.

Murat Türk and Muhammed Burak Yücel contributed equally to this work.

[†]Marcus Maurer sadly passed away before the completion of this manuscript.

Methods: In this prospective, cross-sectional multicenter study, 425 female CSU patients and 370 age-matched controls were recruited from 19 UCARE centers in Türkiye. Dysmenorrhea prevalence and severity were assessed using a numerical scale and symptom scores. Histamine skin prick testing (SPT) was performed to evaluate histamine clearance capacity. Associations between dysmenorrhea, CSU phenotype, antihistamine use, and SPT kinetics were analyzed.

Results: The prevalence and severity of dysmenorrhea were comparable between CSU patients and controls (81.6% vs. 79.5%, $p = 0.244$). However, 95/418 (22.7%) of CSU patients reported increased menstrual pain following CSU onset, and 20/95 (21.1%) of these reported partial relief with antihistamines. CSU patients with worsened dysmenorrhea exhibited significantly shorter histamine SPT positivity durations than those without symptom change (35 vs. 45 min; $p = 0.015$). No correlation was observed between dysmenorrhea severity and total IgE, anti-TPO levels, or urticaria control/activity scores. A moderate negative correlation was found between UAS7 and elapsed time to histamine SPT negativity ($r = -0.389$, $p < 0.001$).

Conclusions: Although overall prevalence and severity of dysmenorrhea were similar in CSU patients and healthy controls, about one in five patients with CSU experienced worsening menstrual pain after disease onset, and only a subset of these patients reported partial improvement with antihistamines. A distinct CSU subgroup with heightened menstrual pain may be characterized by altered histamine dynamics. Whether these patients may benefit from more intensive antihistamine treatment remains uncertain and requires confirmation in future studies; further studies should explore neuroimmune and hormonal mechanisms underlying this overlap.

1 | Introduction

Chronic spontaneous urticaria (CSU) is an inflammatory skin disease predominantly mediated by mast cells, characterized by the occurrence of pruritic wheals, angioedema, or both, persisting for a period exceeding 6 weeks [1]. CSU affects approximately 1% of the global population, with peak onset between the ages of 30 and 50. It has a clear female predominance. While CSU is primarily recognized as a dermatological condition, a growing body of evidence suggests that the disease burden may extend beyond the skin, involving systemic symptoms and comorbid conditions such as psychiatric disorders, autoimmune thyroid disease, and features of metabolic syndrome. Furthermore, some individuals with CSU report extracutaneous symptoms that may not be routinely acknowledged as part of the disease spectrum [2, 3].

Mast cells are central to the pathogenesis of CSU, releasing histamine and other proinflammatory mediators upon activation via IgE- or IgG-mediated pathways [4]. While the role of histamine in generating pruritus and wheals is well established, recent evidence has also highlighted its systemic effects. Histamine receptors are widely expressed in non-cutaneous tissues, including the gastrointestinal tract, central nervous system, and uterus. These distributions suggest that histamine dysregulation could contribute to symptoms beyond the skin, potentially including menstrual pain. Histamine may also contribute to dysmenorrhea via H1 receptor-mediated uterine contractions, potentially explaining increased menstrual pain in female CSU patients [5, 6]. Furthermore, histamine is metabolized by tissue-specific enzymes, such as diamine oxidase (DAO) and histamine-*N*-methyltransferase (HNMT), and inter-individual variability in these pathways may influence symptom severity [7, 8]. Despite the high prevalence of dysmenorrhea among women of reproductive age, its frequency and severity in CSU patients remain unclear. It is also unknown whether the onset of CSU may exacerbate menstrual symptoms and if antihistamines might offer relief through systemic histamine blockade.

While prior studies have suggested that individual variations in histamine skin prick test (SPT) reactivity may reflect differences in histamine sensitivity or clearance capacity, the potential link between histamine kinetics and extra-cutaneous symptoms, such as dysmenorrhea in CSU, has not been investigated [9]. Thus, the primary objective of this study was to compare the prevalence and severity of dysmenorrhea between female CSU patients and age-matched healthy controls. Secondary objectives included evaluating whether dysmenorrhea severity changed after CSU onset and assessing the proportion of patients reporting partial improvement with antihistamines. Exploratory analyses examined histamine SPT kinetics and their associations with disease activity and laboratory parameters.

2 | Methods

HURDLE-I is a prospective, cross-sectional multicenter study that was conducted at 19 different Turkish UCARE [10] centers between January 2024 and June 2024. The study cohort consisted of adult and adolescent female patients of reproductive age diagnosed with CSU and treated according to EAACI/GA^{2}LEN/EDF/WAO guidelines [1]. Age-matched female individuals without a history of CSU or other chronic inflammatory skin disorders were enrolled in the control group.

Demographic data, disease duration, disease phenotype, presence and subtype of inducible urticaria, serum total IgE levels, serum IgG-anti-TPO levels, and antihistamine use data were extracted from the patient records. Patients who reported using NSAIDs during menstrual cycles assessed in the study were excluded to avoid acute pharmacologic modification of pain intensity. Dysmenorrhea severity was assessed using the 0–10 Numeric Rating Scale (NRS), a simple and widely accepted tool for evaluating menstrual pain. The NRS was selected because it is easy for participants to understand, highly practical in large epidemiologic studies, and has been shown to correlate strongly with the visual analog scale (VAS), as demonstrated in the study by Larroy et al., where NRS and VAS scores showed excellent agreement. In addition to the NRS, we used the Verbal Multidimensional Scoring System, a validated four-grade scale (Grades 0–3) that incorporates pain intensity, interference with daily activities, and associated systemic

symptoms. Using both tools allowed for complementary assessment of menstrual pain intensity and functional impact [11, 12]. Of the 425 CSU patients enrolled, dysmenorrhea-change analyses were conducted in 418 patients with complete and eligible menstrual data. Seven patients were excluded due to missing or non-applicable menstrual information. In addition, all patients were asked whether their menstrual pain had changed after CSU onset; if so, intensity of the change (ranging from 1 to 5; very low, low, moderate, marked and severe); and whether antihistamine use relieved their pain; if so, intensity of relief (ranging from 1 to 5; very low, low, moderate, marked and complete). The primary endpoint was dysmenorrhea prevalence and severity in CSU patients versus controls. Secondary endpoints included change in dysmenorrhea after CSU onset and patient-reported response of menstrual pain to antihistamines. Exploratory endpoints included histamine SPT reactivity duration and its correlations with disease activity, IgE levels, and anti-TPO titers. All CSU patients were treated according to EAACI/GA^{2}LEN guideline recommendations, regular use of second-generation H1-antihistamines with physician-directed up-dosing when required for urticaria control. However, antihistamine type, dose, regimen, and dosing relative to the menstrual cycle were not standardized for the purposes of this study, and therefore any patient-reported benefit for dysmenorrhea reflects real-world, heterogeneous usage rather than a controlled intervention.

To assess histamine clearance capacity, standard histamine SPT was performed on the volar forearm using a standard 1 mg/mL histamine hydrochloride solution (Allergopharma, Reinbek, Germany). All patients were antihistamine-free for at least 5 days before the test. The mean diameter of the wheal was measured at 1-min intervals for up to a maximum observation time of 60 min, and the elapsed time until the wheal became negative (i.e., mean diameter < 3 mm) was recorded.

The duration of histamine wheal persistence has been proposed as a functional indicator of individual histamine handling, potentially reflecting variability in degradation pathways such as diamine oxidase (DAO) and histamine-*N*-methyltransferase (HNMT), as well as differences in tissue receptor responsiveness [7, 13, 14]. In this context, extended histamine wheal duration has been used as a simple, non-invasive proxy for impaired histamine degradation in patients with suspected histamine intolerance [13], while large population-based analyses have demonstrated substantial interindividual variability in DAO activity [14]. Together, these data suggest that SPT kinetics may offer an exploratory, functional readout of histamine responsiveness, complementing established systemic biomarkers.

Although all participating UCARE centers followed the same standardized protocol, complete minute-by-minute SPT recordings were available only for a subset of participants due to center-level resource limitations. Therefore, all SPT-related analyses were restricted to this subset of CSU patients and controls with fully documented SPT data.

In this study, Histamine SPT was performed in 289 CSU patients and 286 controls, representing the subset with available SPT data. The control group consisted of voluntary female participants who presented to outpatient clinics for reasons unrelated to dermatologic or inflammatory diseases. Only individuals without CSU or any other mast cell–mediated condition were included. Controls were frequency-matched to CSU patients by age and reproductive status. Women with known gynecologic disorders that may influence menstrual pain (such as endometriosis, adenomyosis, uterine fibroids) or those using hormonal contraception were excluded based on self-report.

This study was approved by the Erciyes University Faculty of Medicine Clinical Research Ethics Committee (approval number: 739, date: 08/11/2023), and written informed consent was obtained from all participants or their legal guardians.

2.1 | Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics v25. Categorical data were summarized as frequencies and percentages, while continuous variables were described using either mean ± standard deviation or median with interquartile range, based on their distribution characteristics. The Shapiro–Wilk test was used to assess the normality of continuous data. Differences between the CSU and control groups were evaluated using Student's *t*-test for variables with normal distribution and the Mann–Whitney *U* test for those not meeting normality assumptions. Categorical variables were compared using either the chi-squared test or Fisher's exact test as appropriate. The association between the duration of SPT reactivity and dysmenorrhea severity was assessed using Spearman's rank correlation. Statistical significance was considered as a *p*-value less than 0.05. Analyses comparing antihistamine-responsive and non-responsive patients were restricted to the subset of CSU patients who underwent histamine SPT and had complete dysmenorrhea and antihistamine response data.

3 | Results

3.1 | Study Participants

A total of 795 female participants of reproductive age were included in the study, with 425 patients in the CSU group and 370 individuals in the healthy control group. The median age was comparable between the groups (29 [22–39] vs. 29 [23–39]; $p = 0.59$). Among the CSU patients, 77% had isolated CSU, and 23% had CSU with comorbid chronic inducible urticaria (CIndU). Of those with CIndU, 73%, 9%, 8%, 7%, and 3% had symptomatic dermographism, cold urticaria, cholinergic urticaria, heat urticaria, and delayed pressure urticaria, respectively. Angioedema was reported in 37.2% of CSU patients (Table 1).

3.2 | Dysmenorrhea Frequency and Severity

The prevalence of dysmenorrhea did not differ significantly between the CSU and control groups (347/425 [81.6%] vs. 294/370 [79.5%], $p = 0.244$). Likewise, dysmenorrhea severity

TABLE 1 | Demographic and clinical characteristics of the study participants.

	Healthy controls ($N=370$)	CSU patients ($N=425$)
Age; median (IQR)	29 (22–39)	29 (22–39)
UAS7; median (IQR)	/	19 (7–29.5)
UCT; median (IQR)	/	8 (4–12)
Urticaria type; *n* (%)		
Isolated CSU	/	328 (77)
CSU with CIndU		97 (23)
Presence of angioedema; *n* (%)	/	158 (37.2)
Serum total IgE level (IU/mL); median (IQR)	/	134 (47.4–329)
< 100 IU/mL; *n* (%)		172 (42.3)
> 100 IU/mL; *n* (%)		235 (57.7)
Serum IgG-anti-TPO level (U/mL); median (IQR)	/	9.2 (1–29)

Abbreviations: CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; IQR, interquartile range; UAS7, urticaria activity score for 7 days; UCT, urticaria control test.

TABLE 2 | Comparison of dysmenorrhea prevalence and severity in control versus CSU groups.

Parameters	Healthy controls ($N=370$)	CSU patients ($N=425$)	*p*
Overall dysmenorrhea frequency; *n* (%)	294 (79.5%)	347 (81.6%)	0.244
Dysmenorrhea severity on NRS; median (IQR)	5 (3–7)	5 (3–7)	0.976
Dysmenorrhea severity on verbal multidimensional scoring system; *n* (%)			
Grade 0 (menstruation is not painful and daily activity is not affected)	62 (16.8)	86 (20.2)	
Grade 1 (mild, menstruation is painful but seldom inhibits normal activity)	147 (39.7)	180 (42.4)	0.356
Grade 2 (moderate, daily activity is affected)	109 (29.5)	105 (24.7)	
Grade 3 (severe, activity clearly inhibited)	46 (12.4)	53 (12.5)	

Abbreviation: NRS, numerical rating scale.

scores on the numeric rating scale (NRS) were similar across groups (5 [3–7] in both; $p=0.976$) (Table 2). We did not observe any correlation between urticaria control test (UCT), UAS7, serum total IgE levels, serum IgG-anti-TPO levels and dysmenorrhea severity scores. The prevalence of dysmenorrhea and dysmenorrhea severity NRS scores were also similar between isolated-urticaria phenotype and urticaria with angioedema phenotype, and also similar between isolated CSU and CSU with CIndU.

However, 95 out of 418 CSU patients (22.7%) reported an increase in dysmenorrhea severity following the onset of CSU. Of these, 26 (26.3%) described a moderate increase, 31 (31.3%) described a marked increase, and 3 (3%) described a severe increase in their symptoms. Nearly one in five of these patients also reported symptomatic relief with antihistamine use (20/95, 21.1%). Of these, 4 (20%), 5 (25%), 7 (35%), and 4 (20%) described very low, low, moderate, and marked relief in their symptoms after antihistamine use, respectively.

3.3 | Histamine Skin Prick Test (SPT) Reactivity

As predefined, these analyses were considered exploratory. SPT with histamine was performed on 289 CSU patients and 286 healthy controls. The overall elapsed time to histamine SPT negativity was not significantly different between CSU patients and controls (40 [30–57.5] vs. 44.5 [30–60] min; $p=0.427$). Similarly, no significant difference was found between patients with and without angioedema (40 [30–57] vs. 41 [30–60] min; $p=0.51$) or between those with and without dysmenorrhea (40 [30–55] vs. 40 [30–60] min; $p=0.985$).

Interestingly, CSU patients who experienced an increase in dysmenorrhea severity after disease onset had significantly shorter SPT reactivity durations compared to those without such an increase (35 [30–46.5] vs. 45 [30–60] min; $p=0.015$). Moreover, patients with isolated-CSU demonstrated shorter reactivity durations than those with CSU + CIndU (40 [30–55] vs. 45 [35.3–60] min; $p=0.011$). In the subset of CSU patients who underwent histamine SPT and had complete dysmenorrhea and antihistamine response data available, the elapsed time to SPT negativity was shorter in the antihistamine-responsive group compared with the non-responsive ones (32 [26–47] vs. 45 [35–50] min; $p=0.12$) (Table 3).

Correlation analysis between UAS7 scores and elapsed time to histamine SPT negativity revealed a moderate negative correlation ($r=-0.389$, $p<0.001$). In contrast, no significant correlation was found between elapsed time to histamine SPT negativity

TABLE 3 | Elapsed time to histamine SPT negativity according to clinical subgroups.

	Elapsed time to histamine SPT negativity (min)	*p*
Healthy controls ($n=286$)	44.5 (30–60)	0.427
CSU patients ($n=289$)	40 (30–57.5)	
Urticaria with angioedema ($n=91$)	40 (30–57)	0.51
Urticaria without angioedema ($n=195$)	41 (30–60)	
Isolated CSU ($n=225$)	40 (30–55)	**0.011**
CSU with CIndU ($n=64$)	45 (35.3–60)	
Presence of dysmenorrhea ($n=233$)	40 (30–55)	0.985
Absence of dysmenorrhea ($n=55$)	40 (30–60)	
Increase in dysmenorrhea severity after the onset of chronic urticaria ($n=52$)	35 (30–46.5)	**0.015**
No change in dysmenorrhea severity after the onset of chronic urticaria ($n=231$)	45 (30–60)	
sgAHs are effective ($n=11$)	32 (26–47)	0.12
sgAHs are not effective ($n=27$)	45 (35–50)	

Note: Analyses restricted to the CSU subgroup with available SPT, dysmenorrhea, and antihistamine response data. *p*-values in bold are statistically significant.
Abbreviation: sgAH, second-generation anti-histamine.

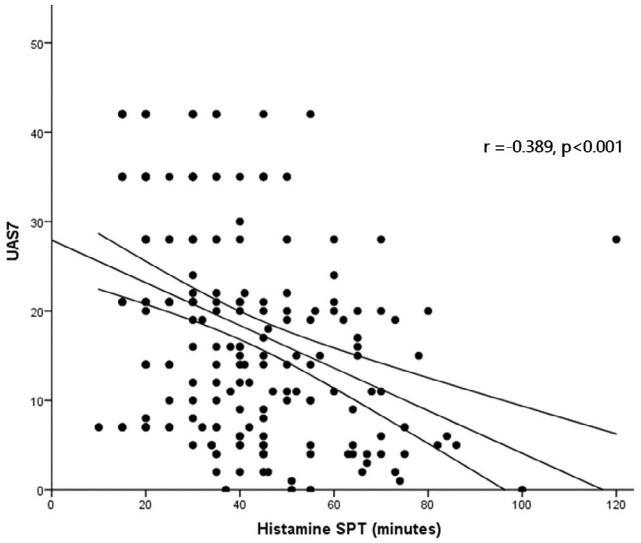

FIGURE 1 | A negative correlation was found between UAS7 scores of the CSU patients and elapsed time to histamine SPT negativity ($n=289$, $r=-0.389$, $p<0.001$).

and dysmenorrhea severity scores, serum total IgE levels, or anti-TPO antibody titers (Figure 1).

4 | Discussion

Our study provides evidence that while the overall prevalence of dysmenorrhea was comparable to healthy controls, approximately one in five patients (22.7%) reported a flare-up of menstrual pain following CSU onset, and only a minority of these patients (21.1%) reported at least partial relief with antihistamines. Notably, those patients experiencing menstrual pain flare-ups exhibited significantly shorter SPT reactivity durations; a similar pattern was seen in patients with higher disease activity and in the isolated CSU phenotype.

Interestingly, the overall prevalence and severity of dysmenorrhea did not differ substantially between CSU patients and healthy controls. However, a significant proportion of patients (22.7%) reported a worsening of dysmenorrhea symptoms following the onset of CSU. This observation implies that CSU may exacerbate menstrual pain in a specific subgroup, possibly due to shared underlying neuroimmune or mast cell–driven mechanisms. In line with this, prior literature has identified dysmenorrhea as a potential general risk factor for chronic pain, independent of pelvic localization. The systematic review by Li et al. demonstrated that women with chronic non-pelvic pain were over twice as likely to report dysmenorrhea, reinforcing the notion that menstrual pain may not be an isolated gynecologic issue but part of a broader sensitization process [5, 15]. The self-reported benefit of antihistamines in a part of CSU patients with worsened dysmenorrhea (21.1%) is compatible with a contribution of histamine-mediated pathways to this overlap, but does not establish a causal relationship. Although a subgroup of patients reported symptom relief with sgAHs, this did not correspond to longer SPT reactivity durations, suggesting that the clinical efficacy of antihistamines for dysmenorrhea may not be directly mediated by skin histamine responsiveness alone. Other factors, such as central sensitization or hormonal modulation, may be involved. Histamine, through its action on H1 receptors, has been shown to mediate both pruritus and nociceptive pain, and is also involved in uterine smooth muscle contraction, thereby potentially contributing to menstrual cramping. Moreover, the influence of sex hormones on mast cell reactivity, especially in reproductive-age women, may contribute to this overlap. Mast cells express estrogen and progesterone receptors, and hormonal fluctuations, particularly during the luteal phase when progesterone peaks, can promote mast cell degranulation, possibly amplifying both urticarial and menstrual pain symptoms [5, 16]. The Global Chronic Urticaria Registry (CURE) has demonstrated that CSU affects not only the skin but also several systemic domains, including mental health, concentration, and particularly sleep quality [17]. In this large cohort, patients with poorly controlled disease (UCT < 12) frequently reported sleep disturbances (59.5%), whereas those with complete control (UCT = 16) showed significantly lower rates of sleep impairment and a markedly better health-related quality of life. These findings emphasize that insufficient CSU control is closely linked to systemic manifestations such as impaired sleep and reduced quality of life, which are known to modulate pain perception and sensitivity. Although dysmenorrhea was

not directly evaluated in CURE, these observations support the hypothesis that similar mechanisms may influence menstrual pain as a systemic symptom in a subset of CSU patients. This indicates that chronic mast cell activation and systemic inflammation in CSU may lower pain thresholds in certain individuals, increasing susceptibility to extracutaneous symptoms like menstrual pain. In summary, these observations support the need for further investigation into the shared neuroimmune circuits and hormonal influences that may underlie the coexistence of CSU and dysmenorrhea [17].

One possible explanation for our findings is that they reflect altered histamine dynamics in a specific subgroup of CSU patients with worsened dysmenorrhea who exhibited significantly shorter histamine SPT reactivity times. These observations raise the hypothesis that certain CSU subgroups may demonstrate distinct histamine dynamics, potentially reflected by shorter SPT reactivity times. Shorter SPT durations could indicate more rapid local histamine degradation via enzymes such as diamine oxidase or histamine-*N*-methyltransferase. Alternatively, they may reflect a shift in histamine bioactivity from the skin toward systemic targets, such as the uterus, suggesting a redistribution of mast cell–driven inflammation. This phenomenon may result in diminished cutaneous responses despite heightened extracutaneous symptoms. It is also plausible that in certain CSU phenotypes, accelerated SPT resolution does not represent lower disease activity but rather a distinct pattern of histaminergic sensitivity with more pronounced systemic manifestations. These interpretations are hypothesis-generating and require validation in mechanistic or longitudinal studies. Together, they support the concept that histamine responsiveness is heterogeneous in CSU and may extend beyond the skin, influencing menstrual and other visceral symptoms. Although speculative, these observations align with previous reports indicating that histamine-induced skin responses can vary depending on individual histamine metabolism capacity, disease-related inflammatory burden [13, 18], and the methodological parameters of SPT measurement, including dose and imaging modality. Notably, a large population-based study reported that nearly half of healthy adults had DAO levels below the conventional threshold for normal histamine degradation despite lacking apparent histamine-related symptoms [14]. These results suggest substantial interindividual variability in systemic histamine clearance capacity, supporting the idea that functional skin-based assessments such as SPT reactivity time may offer a more sensitive indicator for localized histaminergic activity in specific CSU subtypes. Our findings tentatively suggest that SPT kinetics may hold exploratory value as a dynamic biomarker—a hypothesis that warrants validation in future dedicated studies.

Although serum biomarkers such as total IgE and anti-TPO have been associated with distinct endotypes in CSU and may inform therapeutic decisions—particularly regarding omalizumab responsiveness—their direct relationship with cutaneous histamine responsiveness remains unclear. In our study, no significant correlation was found between serum total IgE levels, anti-TPO antibody titers, or dysmenorrhea severity scores and the elapsed time to histamine SPT negativity. Previous reports suggest that static systemic biomarkers might not accurately capture the dynamics of local histamine activity or symptom variability in CSU. A similar finding was demonstrated by Ta et al., who observed no correlation between SPT wheal size or specific IgE levels and reaction severity in a prospective allergy study, highlighting the limitations of relying solely on static immune measures to predict clinical outcomes [19]. Furthermore, Wong and Keith reported that while elevated IgE levels are common in CSU patients, they do not reliably reflect disease activity across individuals [20]. Similarly, Kulthanan et al. found that nearly half of patients had positive SPT responses, but most lacked clinically relevant sensitizations, indicating a disconnect between sensitization and disease burden [21]. Our findings support the idea that histamine SPT reactivity duration may reflect a localized, functional trait that is independent of systemic immune parameters.

In contrast, we observed a moderate but statistically significant negative correlation between UAS7 scores and SPT reactivity time. This finding challenges the traditional notion that prolonged histamine reactivity indicates a higher disease burden. Instead, our results may support the hypothesis that higher disease activity is associated with faster local histamine metabolism. While previous studies have not demonstrated a consistent relationship between traditional SPT parameters (such as wheal diameter or positivity) and disease activity, our study is the first to demonstrate a significant correlation between SPT kinetics and CSU severity as measured by UAS7. This finding raises the possibility that temporal aspects of SPT responses may serve as disease-relevant indicators in certain CSU phenotypes.

Several limitations should be acknowledged when interpreting our findings. First, the sample size, while adequately powered for detecting moderate associations, may limit generalizability across broader CSU populations or less common subtypes. Second, the change in dysmenorrhea after CSU onset was assessed by a retrospective self-report question and, therefore, is subject to recall bias, especially in patients with longer disease duration. Third, although we excluded women with known gynecologic disorders and hormonal contraceptive use based on self-report, we did not systematically collect detailed gynecologic and hormonal data (such as endometriosis, adenomyosis, uterine fibroids, infertility history, or type and duration of hormonal contraception); thus, residual confounding by these factors cannot be ruled out. Fourth, the assessment of SPT reactivity duration was based on a standardized single histamine dose and manual time-point readings; more precise methods, including digital imaging or serial photodocumentation, may provide more accurate kinetic measurements. Fifth, we performed several subgroup and correlation analyses without formal adjustment for multiple comparisons, so especially the SPT-related and phenotype-specific findings should be interpreted as exploratory and hypothesis-generating. Sixth, serum DAO levels and other histamine-degrading enzyme activities were not assessed, which limits our ability to directly correlate skin responses with systemic histamine clearance mechanisms. Moreover, we did not systematically assess other potential systemic symptoms beyond dysmenorrhea, such as headache, flushing, or gastrointestinal complaints, which might also be influenced by histamine-mediated pathways. In addition, the observed partial relief with antihistamines was based solely on subjective patient self-report, without standardized pain assessments, and should therefore be interpreted with caution. Moreover, the assessment of antihistamine-related improvement was not based

on prospective pre- and post-treatment pain measurements, nor were antihistamine type, dose, or timing standardized. Therefore, any reported benefit must be interpreted as subjective, non-causal, and exploratory. Finally, all participating centers were UCARE centers in Turkey, i.e., tertiary urticaria reference centers, which may limit the generalizability of our findings to non-UCARE settings, such as primary or secondary care, and populations with different ethnic or healthcare backgrounds. Future studies incorporating structured gynecologic evaluation and direct measures of systemic histamine metabolism (e.g., DAO, HNMT activity) are needed to test these hypotheses. Finally, because baseline dysmenorrhea severity prior to CSU onset was not prospectively assessed and all symptom changes were based on retrospective recall, causal inference cannot be established. Therefore, our findings should be interpreted as patient-reported temporal associations rather than evidence that CSU independently increases menstrual pain.

5 | Conclusion

In conclusion, while overall prevalence did not differ significantly between CSU patients and controls, one in five patients with CSU reported worsened menstrual pain after disease onset. Furthermore, only a minority of these patients reported partial improvement with antihistamine treatment. Our findings also shed light on a previously underrecognized dimension of CSU pathophysiology by linking histamine SPT kinetics with both cutaneous and extracutaneous symptom profiles. The association between shorter histamine SPT reactivity durations and increased disease activity may indicate variability in functional histamine responsiveness across CSU phenotypes and should be regarded as exploratory and hypothesis-generating.

Acknowledgments

This study was performed by and benefited from the GA2LEN network of urticaria centers of reference and excellence (UCARE; https://ucare-network.com/). This project represents one of the last papers we had the honor of collaborating on with Marcus Maurer, an extraordinary mentor who profoundly inspired and guided all of us. You will be missed, and we will keep loving you.

Funding

The authors have nothing to report.

Conflicts of Interest

Murat Türk is or recently has been a speaker and/or advisor for Abdi İbrahim, AstraZeneca, Chiesi, GSK, Novartis, ROXALL, Vem İlaç. Ragıp Ertaş is or recently has been a speaker and/or advisor for Novartis, Lilly, AbbVie, Pfizer, Eczacıbaşı, and Sanofi. Ozge Sevil Karstarli is or recently was a speaker and/or advisor for Novartis, Lilly, AbbVie, Pfizer, Sanofi, Johnson & Johnson, and UCB. Neslihan Demirel Öğüt is or recently has been a speaker and/or advisor for AbbVie, Abdi İbrahim, Eczacıbaşı, Johnson & Johnson, Lilly, Novartis, ORVA, Pfizer, Sanofi, and UCB. Esra Adışen acted as speaker for Novartis. Torsten Zuberbier has received honoraria for lectures from Amgen, AstraZeneca, AbbVie, ALK–Abelló, Almirall, Astellas, Bayer Health Care, Bencard, Berlin Chemie, FAES Farma, HAL Allergie GmbH, Henkel, Kryolan, Leti, L'Oreal, Meda, Menarini, Merck Sharp & Dohme, Novartis, Nuocor, Pfizer, Sanofi, Stallergenes, Takeda, Teva, UCB, and Uriach; Fees for industry consulting were received from Abivax, Almirall, Bluprint, Celldex, Celltrion, Novartis, and Sanofi; in addition, he declares non-paid organizational affiliations: Committee member, "Allergic Rhinitis and its Impact on Asthma" (ARIA), Member of the Board, German Society for Allergy and Clinical Immunology (DGAKI), Head, European Centre for Allergy Research Foundation (ECARF), President, Global Allergy and Asthma Excellence Network (GA^{2}LEN), and Member, Committee on Allergy Diagnosis and Molecular Allergology, World Allergy Organization (WAO). Emek Kocatürk acted as speaker and advisor for Novartis and Menarini and received funding from Almirall. All other authors declare no conflicts of interest regarding the publication of this article.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. T. Zuberbier, A. H. Abdul Latiff, M. Abuzakouk, et al., "The International EAACI/GA2LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis, and Management of Urticaria," *Allergy* 77, no. 3 (2022): 734–766.

2. P. Pyatilova, Y. Hackler, F. Aulenbacher, et al., "Non-Skin Related Symptoms Are Common in Chronic Spontaneous Urticaria and Linked to Active and Uncontrolled Disease: Results From the Chronic Urticaria Registry," *Journal of Allergy and Clinical Immunology. Practice* 12, no. 7 (2024): 1890–1899.

3. E. Kocatürk and C. Grattan, "Is Chronic Urticaria More Than Skin Deep?," *Clinical and Translational Allergy* 9, no. 1 (2019): 48.

4. I. Yilmaz and T. Murat, "A New Approach for the Classification of Mechanisms of Chronic Spontaneous Urticaria," *Asthma Allergy Immunology* 23, no. 1 (2025): 1–2.

5. E. Kocatürk, I. Podder, A. C. Zenclussen, et al., "Urticaria in Pregnancy and Lactation," *Frontiers in Allergy* 3 (2022): 892673.

6. L. Maintz, V. Schwarzer, T. Bieber, K. van der Ven, and N. Novak, "Effects of Histamine and Diamine Oxidase Activities on Pregnancy: A Critical Review," *Human Reproduction Update* 14, no. 5 (2008): 485–495.

7. Y. Zhao, X. Zhang, H. Jin, L. Chen, J. Ji, and Z. Zhang, "Histamine Intolerance—A Kind of Pseudoallergic Reaction," *Biomolecules* 12, no. 3 (2022): 454.

8. S. Saini, K. E. Rosen, H. J. Hsieh, et al., "A Randomized, Placebo-Controlled, Dose-Ranging Study of Single-Dose Omalizumab in Patients With H1-Antihistamine–Refractory Chronic Idiopathic Urticaria," *Journal of Allergy and Clinical Immunology* 128, no. 3 (2011): 567–573.

9. M. N. Kiran Kumar, B. N. Harish Babu, and Y. P. Venkatesh, "Higher Histamine Sensitivity in Non-Atopic Subjects by Skin Prick Test May Result in Misdiagnosis of Eggplant Allergy," *Immunological Investigations* 38, no. 1 (2009): 93–103.

10. L. Kofler, H. Ulmer, and H. Kofler, "Histamine 50-Skin-Prick Test: A Tool to Diagnose Histamine Intolerance," *International Scholarly Research Notices* 2011, no. 1 (2011): 353045.

11. J. van Odijk, A. Weisheit, M. Arvidsson, N. Miron, B. Nwaru, and L. Ekerljung, "The Use of DAO as a Marker for Histamine Intolerance: Measurements and Determinants in a Large Random Population-Based Survey," *Nutrients* 15, no. 13 (2023): 2887.

12. M. Maurer, M. Metz, C. Bindslev-Jensen, et al., "Definition, Aims, and Implementation of GA 2 LEN Urticaria Centers of Reference and Excellence," *Allergy* 71, no. 8 (2016): 1210–1218.

13. B. Andersch and I. Milsom, "An Epidemiologic Study of Young Women With Dysmenorrhea," *American Journal of Obstetrics and Gynecology* 144, no. 6 (1982): 655–660.

14. A. A. Teherán, L. G. Piñeros, F. Pulido, and M. C. Mejía Guatibonza, "WaLIDD Score, a New Tool to Diagnose Dysmenorrhea and Predict Medical Leave in University Students," *International Journal of Women's Health* 10 (2018): 35–45.

15. R. Li, B. Li, D. A. Kreher, A. R. Benjamin, A. Gubbels, and S. M. Smith, "Association Between Dysmenorrhea and Chronic Pain: A Systematic Review and Meta-Analysis of Population-Based Studies," *American Journal of Obstetrics and Gynecology* 223, no. 3 (2020): 350–371.

16. M. Maurer, M. K. Church, M. Gonçalo, G. Sussman, and M. Sánchez-Borges, "Management and Treatment of Chronic Urticaria (CU)," *Journal of the European Academy of Dermatology and Venereology* 29 (2015): 16–32.

17. P. Kolkhir, P. A. Laires, P. Salameh, et al., "The Benefit of Complete Response to Treatment in Patients With Chronic Spontaneous Urticaria—CURE Results," *Journal of Allergy and Clinical Immunology. Practice* 11, no. 2 (2023): 610–620.

18. J. Butterfield and C. R. Weiler, "The Utility of Measuring Urinary Metabolites of Mast Cell Mediators in Systemic Mastocytosis and Mast Cell Activation Syndrome," *Journal of Allergy and Clinical Immunology. In Practice* 8, no. 8 (2020): 2533–2541.

19. V. Ta, B. Weldon, G. Yu, O. Humblet, S. Neale-May, and K. Nadeau, "Use of Specific IgE and Skin Prick Test to Determine Clinical Reaction Severity," *British Journal of Medicine and Medical Research* 1, no. 4 (2011): 410.

20. M. M. Wong and P. K. Keith, "Presence of Positive Skin Prick Tests to Inhalant Allergens and Markers of T2 Inflammation in Subjects With Chronic Spontaneous Urticaria (CSU): A Systematic Literature Review," *Allergy, Asthma and Clinical Immunology* 16, no. 1 (2020): 72.

21. K. Kulthanan, S. Jiamton, N. Rutnin, M. Insawang, and S. Pinkaew, "Prevalence and Relevance of the Positivity of Skin Prick Testing in Patients With Chronic Urticaria," *Journal of Dermatology* 35, no. 6 (2008): 330–335.