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Symptomatic Dermographism Versus Chronic Spontaneous Urticaria; A Detailed Analysis of Clinical Features, Treatment Responses, and Comorbidities

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ABSTRACT

Objective: Although symptomatic dermographism (SD) is the most common subtype of chronic inducible urticaria (CIndU), little is known about the differences between SD and chronic spontaneous urticaria (CSU). Information about the etiopathogenesis and underlying causes of SD are scarce. In our study, we aimed to evaluate the differences between the SD and CSU in terms of demographic, clinical, laboratory characteristics, and comorbid conditions.

Materials and Methods: This was a retrospective study and we examined the medical records of CSU and SD patients referred to our Urticaria Center of Reference and Excellence center. Differences in demographic and clinical characteristics, laboratory parameters, accompanying conditions, and response to standard doses (single dose) of second-generation antihistamines (sg-AH) between the SD and CSU groups were determined. Treatment responses were evaluated by the urticaria control test (UCT).

Results: A total of 856 patients (231 with SD and 625 with CSU) were included in the analysis. Patients with SD were younger (age; median 34 vs 37; $p<0.001$) and had less accompanying systemic symptoms (4.3% vs 25%; $p<0.001$) than patients with CSU. Systemic diseases (36.7% vs 27.4% vs $p=0.017$), elevated C-reactive protein and erythrocyte sedimentation rate and positive anti-thyroid peroxidase antibody were found to be more frequent in CSU patients compared to SD patients ($p<0.001$, $p=0.003$, $p=0.03$). Accompanying atopy, stress and infections were found to be similar between the two groups ($p>0.05$; for all). Patients with SD showed better response to standard doses of sg-AHs than patients with CSU (UCT ≥12 in 59.6% vs 47.4%; $p=0.005$).

Conclusion: SD differs from CSU in terms of fewer systemic components and better response to antihistamines.

Keywords: Chronic inducible urticaria, chronic spontaneous urticaria, symptomatic dermographism, treatment response

INTRODUCTION

Chronic urticaria (CU) is classified into spontaneous and inducible urticaria. Chronic inducible urticaria (CIndU) is characterized by recurrent appearance of hives and/or angioedema for more than 6 weeks in response to specific eliciting triggers (1-3). Symptomatic dermographism (SD) (dermographic urticaria, urticaria factitia) is the most common subtype of CIndU, which is characterized by strip-shaped itchy wheals on areas that are exposed to scratching, rubbing, and scrubbing due to shearing forces (2-4). Wheals appear within seconds to minutes after the provocation, and lesions last 5 minutes to 30 minutes (4). SD occurs in approximately 1-5% of the population, is seen in young adults (2,5,6), and the disease has a long course (5,7). Dermographism is thought to be idiopathic but it may be seen in people with diabetes, hyper-hypothyroidism, menopause, pregnancy, and stress or may be trig-

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gered by bacterial, fungal, or viral infections; Helicobacter pylori (H. pylori), scabies, insect bites or some drugs. (3,8,9). A recent case-control study has shown that rates of asthma, allergic rhinitis, atopy, and thyroid disease were found to be higher in patients with SD than CSU patients (10). All CIndU subtypes have distinct characteristics (11) and different treatment responses (12). Although SD is the most common subtype of CIndU, there are few studies showing the demographic findings, clinical and laboratory characteristics, treatment responses, and comorbid conditions in SD patients (9,10,13,14). CSU and SD not only differ clinically in that a shearing force is needed for SD to come out while CSU is spontaneous, the wheals follow the configuration of the shearing force (generally linear pattern) in SD while CSU wheals do not follow a specific pattern. When it comes to the pathophysiological differences, there is little information about the pathophysiology of SD whilst a mechanism which includes autoallergic IgE-mediated mast cell activation is suggested (15), whereas for CSU both IgG-mediated and IgE-mediated autoimmune mechanisms are involved (11,16). In this study, we aimed to determine the demographic findings, clinical and laboratory characteristics, treatment responses, and comorbid conditions in SD compared to CSU.

MATERIALS and METHODS

This was a cross-sectional retrospective study that included 856 patients (625 CSU and 231 SD) who were referred to our UCARE (17) center between January 2013 and July 2019. This study was approved by the Institutional Ethics Committee (number of IRB 2021;163). All patients with SD and isolated CSU that were referred within the defined time period were included in the analyses. Patients with CSU accompanying CIndUs were excluded from the analysis.

Demographic characteristics including age, sex, disease duration, family history, accompanying angioedema, atopy, lesion duration and appearance time of the day, systemic symptoms, triggering factors, gastrointestinal disease, psychological disorders, stress, accompanying infections and presence of systemic disorders, and autoimmune thyroiditis were noted in both groups. Atopy was defined as having one or more of conditions such as asthma, eczema, or rhinitis.

Laboratory results including C-reactive protein (CRP) values (high CRP was considered for values ≥5 mg/L), erythrocyte sedimentation rate (ESR) (elevated ESR was considered for values ≥20 mm/h), anti-thyroid peroxidase antibody (anti-TPO-IgG), anti-thyroglobulin antibody (anti-TG-IgG) (positive anti-TPO/anti-TG were defined for values ≥34 IU/mL), total IgE (high total IgE was considered for values ≥43 IU/mL), and H. pylori stool antigen test results were retrieved from the patients' files.

Baseline Urticaria Control Test (UCT), response to standard doses (single dose) of second-generation antihistamines (sg-AH), emergency referrals, and short-term systemic steroid use were extracted from patient charts.

Response to sg-AH was determined with the Urticaria control test (UCT) (18). UCT is a 4-question tool, and each question has 5 options (0-4 points). The total UCT score is the sum of all 4 individual item scores (0-16 points). A score of ≥12 was defined as a responder and a score of <12 points was defined as a non-responder in our study.

Demographic characteristics, laboratory findings, accompanying conditions, and standard dose antihistamine responses were compared between patients with SD and CSU.

Statistical Analyses

Statistical analyses were performed by using SPSS software version 27.0 (Statistical Package for Social Science). All numerical variables were reported as the median, minimum, maximum, interquartile range-IQR (25^{th}-75^{th} percentiles), frequency and percentages.

Age, disease duration, lesion duration, CRP and ESR, total IgE, and baseline UCT levels of the SD and CSU groups were analyzed with the Mann-Whitney U test. The comparison of gender, positive family history, accompanying atopy, lesion appearance time, systemic symptoms, triggering factors; laboratory results including elevated CRP, ESR, total IgE, positive anti-TPO and TG, positive H. pylori antigen; and accompanying conditions such as AIT, systemic diseases, gastrointestinal disease, psychological disorders, stress, accompanying infections, number of emergency referrals, and short-term systemic steroid use as well as the comparison of the response to standard doses of sgAHs in the SD and CSU groups were analyzed with the Pearson chi-squared test or Fisher exact test. P values lower than 0.05 were considered as significant.

RESULTS

All demographic and clinical characteristics of patients with CSU and SD are shown in Table I. The patients with SD were younger (median 34 vs 37; p<0.001) than the patients with CSU but the female dominance was similar between the two groups (p=0.817). Disease duration was similar between the two groups (p=0.797); however, the duration of individual lesion (median; 20 vs 150 minutes; p<0.001) was lower in patients with SD than patients with CSU. Lesions appear more in the night time and in the morning in CSU patients compared to SD patients (62.9% vs 48.2%; p=0.001, 7.4% vs 2.6%; p=0.017). Accompanying atopy was more frequent in SD patients, although the difference was not significant (31% vs 24.8; p=0.084). Patients with CSU reported more accompanying systemic symptoms such as arthralgia and malaise (25% vs 4.3% vs p<0.001) than patients with SD (Table I).

Elevated CRP (≥5 IU/ml) (40.7% vs 19.1%; p<0.001), elevated ESR (≥20 IU/ml) (38.7% vs 22.6%; p=0.003) and anti-TPO positivity (21.6% vs 12.7%; p=0.03) were more frequent in CSU patients than SD patients, while total IgE levels (≥43 IU/mL) were found to be similar between the two groups (p=0.236) (Table II).

Accompanying psychological conditions, stress, gastrointestinal disorders and accompanying infections were found to be similar between the two groups (p>0.05; for all). However, systemic diseases were found to be more frequent in CSU patients than SD patients (36.7% vs 27.4%; p=0.017) (Table III).

Baseline UCT scores were lower in CSU patients (median; 7 vs 8; p=0.033) and presentations to emergency departments (69.7%, n=253 vs 47.9%, n=23; p=0.003), and systemic steroid treatment (69.7%, n=260 vs 36.6%, n=37; p<0.001) were higher in CSU patients than SD patients. Patients with SD showed better response to standard doses of sgAHs than patients with CSU (59.6%, n=106 vs 47.4%, n=260; p=0.005) (Figure 1).

Table I: Demographic and clinical characteristics of patients with chronic spontaneous urticaria and symptomatic dermographism.

	Total n=856	CSU n=625 (73%)	SD n=231(27%)	p-value
Age (years)				p<0.001[a]
Median (min-max)	36 (3-85)	37 (3-85)	34 (8-74)	
Interquartile range-IQR (25th-75th percentiles) n=825	27-47	28-50	25-43	
Gender, n (%)				0.817[b]
Female	584 (68.2)	425 (68)	159 (68.8)	
Male	272 (31.8)	200 (32)	72 (31.2)	
Disease duration (mos)				0.797[a]
Median (min-max)	12 (1-600)	12 (1-600)	12 (1-240)	
Interquartile range-IQR (25th-75th percentiles) n=830	6-48	6-48	6-12	
Family history, n (%), n=748	139 (18.6)	95 (17.4)	44 (21.9)	0.159[b]
Accompanying angioedema, n (%), n=586	349 (40.8)	349 (59.6)	-	-
Accompanying atopy, n (%), n=763	202 (26.5)	137 (24.8)	65 (31)	0.084[b]
Lesion duration time (min)				p<0.001[a]
Median (min-max)	100 (1-1440)	150 (3-1440)	20 (1-1440)	
Interquartile range-IQR (25th-75th percentiles) n=545	20-300	60-480	10-60	
Lesion appearance time, n (%), n=732				
Evening	432 (59)	339(62.9)	93 (48.2)	p<0.001[b]
Morning	45 (6.1)	40 (7.4)	5 (2.6)	0.017[b]
Daytime	66 (9)	48 (8.9)	18 (9.3)	0.861[b]
Systemic symptoms, n (%), n=684	142 (20.8)	136 (25)	6 (4.3)	p<0.001[b]
Triggering factor, n (%), n=565	279 (49.4)	202 (47.2)	77 (56.2)	0.066[b]

CSU: Chronic spontaneous urticaria, **max:** Maximum, **min:** Minimum, **mos:** Months, **SD:** Symptomatic dermographism
[a]Mann-Whitney U test [b]Pearson chi-squared test

Table II: Laboratory parameters of patients with chronic spontaneous urticaria and symptomatic dermographism.

	Total	CSU	SD	p-value
CRP				0.025[a]
Median (min-max)	3.5 (0-192)	4.11 (0-192)	3.3 (0-17.7)	
Interquartile range-IQR (25^{th}-75^{th} percentiles) n=345	3-7.78	3-8.57	3-5.35	
High levels of CRP (≥5 mg/L), n (%), n=348	147 (34.8)	125 (40.7)	22 (19.1)	p<0.001[b]
ESR				0.016[a]
Median (min-max)	15 (0-91)	17 (0-91)	12.5 (0-61)	
Interquartile range-IQR (25^{th}-75^{th} percentiles) n=333	10-26	10-27	8-20.25	
High levels of ESR (≥20 mm/h), n (%), n=380	130 (34.2)	106 (38.7)	24 (22.6)	0.003[b]
Positive Anti-TPO (≥34 IU/mL), n (%)	93 (19.3)	77 (21.6)	16 (12.7)	0.03[b]
Positive Anti-TG (≥34 IU/mL), n (%), n=349	58 (16.6)	45 (18.4)	13 (12.4)	0.163[b]
AIT, n (%), n=475	49 (10.3)	34 (9.4)	15 (13.2)	0.252[b]
Positive H.pylori antigen, n (%), n=256	140 (54.7)	104 (55.3)	37 (54.4)	0.897[b]
Total IgE level				0.236[a]
Median (min-max)	152 (0-7158)	144.5 (0-7158)	173 (11-1172)	
Interquartile range-IQR (25^{th}-75^{th} percentiles) n=473	67.5-311.85	63-312.27	85.5-313.5	
IgE≥43 (IU/mL), n (%), n=503	395 (78.5)	298 (79)	97 (77)	0.626[b]

AIT: Autoimmune thyroiditis, **anti-TG:** Anti thyroglobulin antibody, **anti-TPO:** Anti thyroid peroxidase antibody, **CRP:** C-reactive protein, **CSU:** Chronic spontaneous urticaria, **ESR:** Erythrocyte sedimentation rate, **H. pylori:** Helicobacter pylori, **IgE:** Immunglobulin E, **max:** Maximum, **min:** Minimum, **SD:** Symptomatic dermographism
[a]Mann-Whitney U test
[b]Pearson chi-squared test

Table III: Accompanying conditions in patients with chronic spontaneous urticaria and symptomatic dermographism.

	Total	CSU	SD	p-value
Stomach problems, n (%), n=771	281 (36.4)	209 (37.5)	72 (33.8)	0.346[b]
Intestinal disease, n (%), n=589	82 (13.9)	68 (14.9)	14 (10.4)	0.186[b]
Psychological conditions, n (%), n=763	528 (69.2)	382 (69.3)	146 (68.9)	0.902[b]
Stress, n (%), n=513	278 (52.2)	198 (54)	80 (54.8)	0.863[b]
Systemic disease, n (%), n=757	259 (34.2)	204 (36.7)	55 (27.4)	0.017[b]
Accompanying infections, n (%), n=760	310 (40.8)	224 (40.7)	86 (41.1)	0.901[b]
Tooth cavities	175 (23)	129 (23.4)	46 (22)	0.682[b]
Urinary tract infections	35 (4.6)	21 (3.8)	14 (6.7)	0.09[b]
Sinusitis	50 (6.6)	40 (7.3)	10 (4.8)	0.219[b]
Combined infections*	28 (3.7)	24 (4.4)	4 (1.9)	0.111[b]
GIS infections	12 (1.6)	8 (1.5)	4 (1.9)	0.475[c]

CSU: Chronic spontaneous urticaria, **GIS:** Gastrointestinal system, **SD:** Symptomatic dermographism
*Combined infection" is the presence of two or more concurrent infections, such as tooth cavities, sinusitis, urinary tract infections, or gastrointestinal system infections
[b]Pearson chi-squared test [c]Fisher exact test

DISCUSSION

In the current study, we found distinct characteristics in SD versus CSU patients regarding patient characteristics, clinical presentation, some of the associated conditions, laboratory findings, and treatment responses.

Patients with SD were found to be younger compared to CSU patients (median; age 34 vs 37 years; p<0.001) which is consistent with the general knowledge that SD generally presents in young adults, during the 2^{nd} or 3^{th} decades of life (13), while CSU patients tend to have an older age of

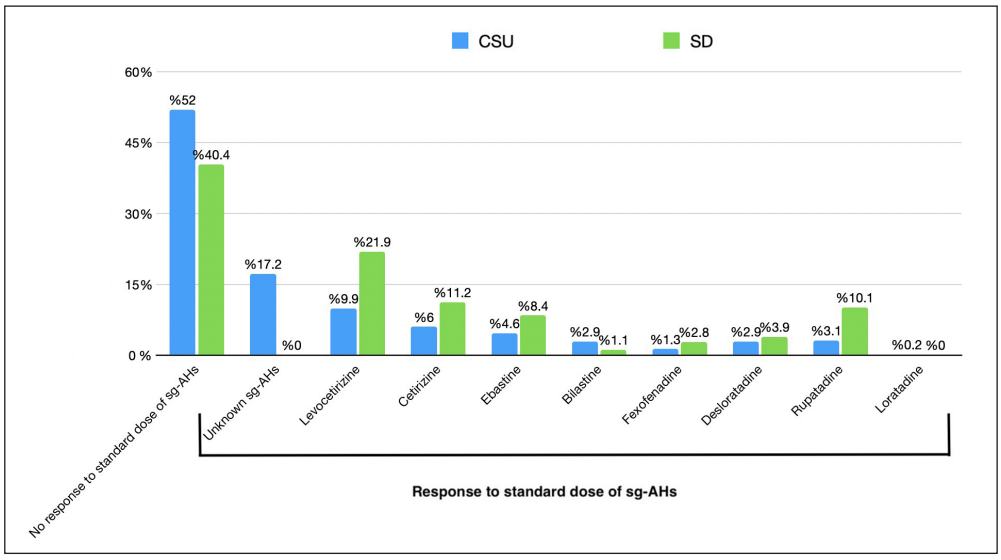

Figure 1. Patients with symptomatic dermographism showed better response to standard doses of sgAHs than patients with chronic spontaneous urticaria

onset usually between 30-50 years (19). As expected, in our study, SD had a shorter duration of individual lesions than those with CSU (median 20 vs 150 minutes; p<0.001). Lesions in SD typically develop quickly and persist for 15 to 30 minutes (20). In a study, wheals were reported to persist for 5-30 min in 47% of the patients and for 30-60 min in 20% (13). We also found that lesions mostly appeared at evening time in both groups, though significantly higher in CSU patients than SD patients. A study of SD showed that 81% of the cases reported their symptoms to worsen in the evening (13), while patients with CSU reported to have nocturnal symptoms (21). However, another study showed that CU patients mostly bothered by symptoms in the evening (34%) (22). Accompanying systemic symptoms were lower in SD patients than patients with CSU in our patient population. It has been reported that 31.2% of CSU patients had one or more systemic symptoms (23). In a study, 37.1% of the patients of SD reported headaches, while 62.5% reported fatigue as systemic symptoms (13). Since CSU patients with systemic complaints had been reported to have greater baseline serum tryptase levels (24) and increased levels of plasma histamine could lead to concentration-related histamine-mediated symptoms (25), we believe that the reason for less systemic complaints in SD is associated with lower histamine and tryptase levels in the bloodstream due to the localized and short-lasting nature of the lesions. However, there are no studies comparing the histamine and tryptase levels of different subtypes of CU. Although an increase in blood histamine in patients with SD has been reported in two studies (26,27), a comparison with CSU was not mentioned.

In our study, both SD and CSU groups exhibited a female predominance (68.8% vs 68%), which is consistent with the findings reported in the literature. All types of CU are more prevalent in females, with the exception of cholinergic urticaria patients (19). Disease duration was similar between the SD and CSU groups in our study population. Previous studies reported that SD generally lasts for long years, $6^{¼\text{-}1/2}$ years on average (2,7,13,28), while disease duration is 1-5 years in CSU (29), suggesting that SD might have a longer disease duration.

Systemic comorbid diseases were more frequent in CSU patients than SD patients in our study population. Atopic, autoimmune, and psychiatric disorders are prevalent comorbidities, while cardiovascular disease, metabolic syndrome and other comorbidities have also been reported (30). CSU and metabolic syndrome are associated with low-grade inflammation (31). Long-lasting and uncontrolled disease is found to be associated with multimorbidities in CSU (32), suggesting that more and longer lasting inflammation may be associated with more systemic consequences. Systemic comorbidities were also found in patients with SD in our study, but lesser than in the CSU group, and can be due to lower levels of many cytokines and chemokines that are released into the circulation (33). Likewise, admissions to emergency and systemic steroid use were higher in the CSU group than the

SD group. These findings show that CSU manifests as a more severe disease phenotype. The reason is probably the infiltration seen in CSU, whereas there is no cellular infiltrate in SD (34).

SD patients reported more accompanying atopy in our study population than CSU patients did, although the difference is not significant. Accompanying atopy was reported to be higher in patients with SD compared to patients with CSU (OR: 8.81, p<0.001) in a recent case-control study. The rates of asthma (OR: 1.79, p = 0.036), and allergic rhinitis (OR: 6.03, p< 0.001) were also reported to be higher in patients with SD than patients with CSU (10). Schoepke et al. (13) reported that 48% of patients have concomitant allergic disease, while other studies revealed that 12.5% and 63.7% of the patients with SD were atopic (9,14).

In our study, elevated CRP and ESR levels and anti-TPO positivity were significantly higher in the CSU group than the SD group. Higher disease activity, longer disease duration, higher rates of concomitant autoimmune diseases such as Hashimoto, anti-TPO positivity, lower total IgE levels, higher rates of eosinopenia and basopenia, and poor response to AHs favors type IIb autoimmune urticaria while higher rates of concomitant allergic diseases, and normal or high total IgE levels favors type I autoimmunity (35,36). Our findings suggest that CSU patients tend to show a more type IIb autoimmune CSU profile, while it is not possible to suggest for a particular endotype for SD patients. The reason is that total IgE levels and atopy rates were similar between the SD and CSU groups. However, although the pathogenesis is unclear, autoallergic IgE-mediated mast cell activation has been suggested in SD (19).

SD patients had similar frequency of AIT and anti-TG positivity as the CSU patients in our study population, although positive anti-TPO levels were higher in the CSU patients than the SD patients. There is a strong link between CSU and elevated levels of IgG antithyroid autoantibodies. In a systemic review, increased levels of IgG-anti-TG in CSU were reported at 0%-42.6%. Other studies have reported increased levels of IgG-anti-TPO in 0%-60.5% of the patients (37). CSU is associated with autoimmune thyroid disease in about 4.3%-57.4% of the patients (38). Interestingly, a recent case-control study has shown that rates of thyroid disease (OR: 1.78, p = 0.039) and thyroid antibody positivity (OR: 1.93, p = 0.039) were higher in patients with SD than CSU patients (10).

Gastrointestinal comorbidities, H. pylori antigen positivity, and accompanying infections were found to be similar between SD and CSU patients in our study population. While H. pylori and focal bacterial infections have been reported in up to 77% of patients with CSU (19), the infection rate was 34.3% (i.e. dental caries, upper respiratory tract infection, and positive HBsAg) and dyspepsia rate was 14.3% (39) in SD.

Psychological conditions (68.9% vs 69.3%), and stress (54.8% vs 54%) affected the SD and CSU groups similarly in our study population. The overall prevalence of any psychological condition was reported to be 31.6% in CU (40) with depression and anxiety being present in up to 60% of the patients with CSU (19). Association of SD with anxiety and stress has been reported (41). A study has reported that 44% of SD patients claimed experiencing stress-induced acute episodes (13), while other studies showed frequencies of 30% (9) and 33% (42).

We found that patients with SD had a better response to a standard dose of sgAHs than patients with CSU (59.6% vs 47.4%), which we think is higher than the reported response rates with SD patients of 25.9% (43), 54.6% (12) and 28.9% (44). About 50% of CSU cases respond to standard dose sgAHs (45), while this response rate was reported to be 21% (46), 32.9% (42) and 51.6% (12) in CINDU patients.

Limitations

This study has several notable strengths. It includes a large sample size of 856 patients, providing robust statistical power and improving the generalizability of its findings. The detailed comparison between SD and CSU offers valuable insights into the differences in demographic, clinical, and laboratory characteristics, as well as treatment responses. By utilizing real-world data from a specialized Urticaria Center of Reference and Excellence, the study reflects practical clinical outcomes. Moreover, the evaluation of treatment responses using a validated tool like the Urticaria Control Test (UCT) and the exploration of comorbidities, such as autoimmune thyroiditis and psychological disorders, further enhance the clinical relevance of the findings.

However, there are also limitations. The retrospective design may introduce selection bias and limitations in data consistency. Additionally, as a single-center study, the findings may not be fully generalizable to other regions

or clinical settings. The absence of key biochemical markers, such as tryptase and histamine levels, limits the understanding of the underlying pathophysiology. Furthermore, the study does not deeply explore molecular mechanisms, and its cross-sectional nature precludes the evaluation of long-term outcomes or disease progression. Lastly, the lack of a placebo-controlled or comparative treatment arm restricts the ability to draw definitive conclusions about treatment efficacy.

CONCLUSIONS

Our study identifies significant differences between symptomatic dermographism (SD) and chronic spontaneous urticaria (CSU) in terms of patient characteristics, clinical presentation, associated conditions, laboratory findings, and treatment responses. These findings suggest that different pathomechanisms may underlie these chronic urticaria subtypes. For instance, the younger age of SD patients and the shorter duration of individual lesions contrast with the older age and longer lesion duration observed in CSU patients. Additionally, systemic symptoms and elevated serum markers indicative of inflammation and autoimmunity are more prevalent in CSU, highlighting a potential type IIb autoimmune profile.

Despite these insights, the precise pathomechanistic pathways distinguishing SD from CSU remain unclear. Our results underscore the necessity for further research to elucidate these distinct mechanisms. Comprehensive studies comparing histamine and tryptase levels, as well as other immunological markers, across different urticaria subtypes will be crucial in advancing our understanding. Such studies will not only help in identifying the specific pathways involved but also pave the way for more targeted and effective therapeutic strategies.

Conflict of Interest

Emek Kocaturk has served for the advisory board and given lectures for Novartis, Sanofi, Menarini, Abdi İbrahim, Pfizer, and La Roche Posey. Other authors have no conflicts of interest.

The manuscript has been read and approved by all the authors, and each author believes that the manuscript represents honest work.

Ethics Approval

The study was approved by the ethics review board of Okmeydanı Training and Research Hospital (number of IRB: 163;2021)

Authorship Contributions

Concept: **Pelin Kuteyla Can, Emek Kocaturk,** Design: **Pelin Kuteyla Can, Emek Kocaturk,** Data collection or processing: **Pelin Kuteyla Can, Emek Kocaturk,** Analysis or Interpretation: **Pelin Kuteyla Can, Emek Kocaturk,** Literature search: **Pelin Kuteyla Can, Emek Kocaturk,** Writing: **Pelin Kuteyla Can, Emek Kocaturk,** Approval: **Pelin Kuteyla Can, Emek Kocaturk.**

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