SHORT COMMUNICATION

Dermatological Comorbidities in Patients with Acute Urticaria

Eli MAGEN[1,2], Eugene MERZON[1,3], Ilan GREEN[1,4], Shlomo VINKER[1,4] and Ariel ISRAEL[1,4]
[1]Leumit Health Services, Tel Aviv-Yafo, [2]Medicine A Department, Assuta Ashdod University Hospital Faculty of Health Sciences, Ben-Gurion University, 8410501 Beer-Sheba, [3]Adelson School of Medicine, Ariel University, Ariel and [4]Department of Family Medicine, Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv-Yafo, Israel. E-mail: allergologycom@gmail.com
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Acute urticaria (AU) is a prevalent skin disorder affecting 12–22% of the general population worldwide(1, 2). Despite significant research on AU, its potential associations with other dermatological comorbidities have received limited attention (3). Prior studies have focused mainly on understanding AU's pathophysiology and management, underscoring the need to explore its links with other dermatological conditions (4).

MATERIALS AND METHODS

This study utilized data from Leumit Health Services (LHS), one of Israel's healthcare providers. LHS has used centrally managed electronic health records (EHR) for the last 20 years. The LHS EHR database include demographic data, physical measures, laboratory test results, medication prescriptions and purchases, and diagnosed conditions, documented by physicians according to the International Classification of Diseases 9th Revision (ICD-9). The study cohort comprised more than 1,000,000 individuals insured by LHS for at least 2 years.

The study employed ICD-9 codes to identify cases of AU. Specifically, the codes 708.0, 708.1, 708.8, and 708.9 were utilized, which encompass cases of AU. To ensure the specificity of the current study AU cohort, individuals with at least 2 ICD-9 diagnosis codes of 708.0, 708.1, 708.8, or 708.9 recorded at least 6 weeks apart were excluded from the study. Within this cohort, the AU group (n=72,851) included patients with a documented AU diagnosis, while the control group (n=291,404) comprised individuals without AU. Rigorous matching based on sex, age and ethnic group was performed to ensure comparability between the 2 groups. LHS electronic health records and ICD-9 codes were used to compare the lifelong prevalence of dermatological comorbidities.

Statistical analysis

Differences in demographic and clinical characteristics between groups were analysed using independent sample t-tests for normally-distributed continuous variables. For categorical variables, proportions were tested using Fisher's exact test. Odds ratios and 95% confidence intervals (95% CIs) were calculated. All statistical analyses were conducted using R software version 4.0.2 (R Foundation, https://cran.r-project.org).

Reults

The results of the study are presented in the **Table I**. No significant differences were observed between the 2 groups regarding sex and ethnic distribution, with most participants being female (58.7%). Similarly, the mean age in both groups was approximately 26.9±22.7 years (p=0.932). To further dissect age-related trends, participants were categorized into specific age groups. These groups included paediatric categories (0–2, 3–9, 10–18 years), young adults (19–29, 30–39 years), middle-aged adults (40–49, 50–59 years), and senior adults (60–69, 70–79, 80–89 years). For all age categories, the distribution was relatively comparable between the AU and control groups (p-values close to 1).

Table I. Lifelong prevalence of dermatological comorbidities in patients with and without acute urticaria

Dermatological comorbidities	Acute urticaria (N = 72,851) ***n*** (%)	Control (N = 291,404) ***n*** (%)	***p*-value**	Odds ratio (OR) [95% CI]
Inflammatory skin diseases				
Atopic dermatitis	13,943 (19.2)	36,562 (12.6)	<0.001	1.65 [1.61–1.69]
Psoriasis	3,122 (4.29)	9,495 (3.26)	<0.001	1.33 [1.28–1.39]
Contact dermatitis	23,972 (32.9)	63,729 (21.9)	<0.001	1.75 [1.72–1.78]
Seborrhoeic dermatitis	7,825 (10.75)	24,548 (8.43)	<0.001	1.31 [1.27–1.34]
Dermatitis herpetiformis	149 (0.20)	341 (0.12)	<0.001	1.75 [1.43–2.13]
Lichen planus	442 (0.61)	1,223 (0.42)	<0.001	1.45 [1.30–1.62]
Pityriasis rosea	1,754 (2.41)	4,860 (1.67)	<0.001	1.45 [1.38–1.54]
Erythema multiforme	302 (0.41)	409 (0.14)	<0.001	2.96 [2.54–3.45]
Stevens-Johnson syndrome	10 (0.01)	12 (0.004)	0.006	3.33 [1.29–8.42]
Acne	14,424 (19.8)	48,696 (16.7)	<0.001	1.23 [1.21–1.26]
Rosacea	912 (1.25)	2,622 (0.90)	<0.001	1.40 [1.29–1.51]
Erythema nodosum	177 (0.24)	448 (0.15)	<0.001	1.58 [1.32–1.89]
Hidradenitis suppurativa	128 (0.18)	354 (0.12)	<0.001	1.45 [1.17–1.78]
Infectious skin diseases				
Impetigo	7,162 (9.84)	23,964 (8.23)	<0.001	1.22 [1.18–1.25]
Cellulitis or abscess of skin	20,993 (28.8)	65,615 (22.5)	<0.001	1.39 [1.37–1.42]
Erysipelas	787 (1.08)	2,414 (0.83)	<0.001	1.31 [1.20–1.42]
Dermatophytosis (ringworm)	24,140 (33.2)	79,210 (27.2)	<0.001	1.33 [1.30–1.35]
Candidiasis	1,778 (2.44)	4,999 (1.72)	<0.001	1.43 [1.36–1.51]
Tinea versicolor	9,684 (13.3)	30,535 (10.5)	<0.001	1.31 [1.28–1.34]
Herpes simplex	10,516 (14.4)	32,592 (11.2)	<0.001	1.34 [1.31–1.37]
Herpes zoster	4,598 (6.32)	14,505 (4.98)	<0.001	1.29 [1.24–1.33]
Molluscum contagiosum	4,806 (6.60)	17,050 (5.85)	<0.001	1.14 [1.10–1.17]
Viral warts	20,443 (28.1)	70,295 (24.1)	<0.001	1.23 [1.20–1.25]
Scabies	2,227 (3.06)	5,164 (1.77)	<0.001	1.75 [1.66–1.84]
Pediculosis	943 (1.30)	3,065 (1.05)	<0.001	1.23 [1.15–1.33]
Autoimmune diseases				
Lupus erythematosus (systemic)	176 (0.24)	533 (0.18)	<0.001	1.32 [1.11–1.57]
Lupus erythematosus (discoid)	47 (0.065)	94 (0.032)	<0.001	2.00 [1.38–2.87]
Dermatomyositis	91 (0.125)	274 (0.094)	0.022	1.33 [1.04–1.69]
Scleroderma (systemic)	55 (0.076)	146 (0.050)	0.012	1.51 [1.08–2.07]
Scleroderma (localized)	25 (0.03)	66 (0.02)	0.087	1.52 [0.92–2.43]
Cutaneous vasculitis	92 (0.13)	143 (0.05)	<0.001	2.58 [1.96–3.37]
Pemphigus	42 (0.058)	120 (0.041)	0.062	1.40 [0.96–2.01]
Bullous pemphigoid	58 (0.080)	110 (0.038)	<0.001	2.11 [1.51–2.93]
Dermatitis herpetiformis	149 (0.20)	341 (0.12)	<0.001	1.75 [1.43–2.13]
Alopecia areata	1,401 (1.92)	4,526 (1.55)	<0.001	1.24 [1.17–1.32]
Vitiligo	566 (0.78)	1,748 (0.60)	<0.001	1.30 [1.18–1.43]
Neoplastic skin diseases				
Mycosis fungoides	121 (0.06)	335 (0.04)	<0.001	1.45 [1.16–1.78]
Melanoma	217 (0.30)	773 (0.27)	0.131	1.12 [0.96–1.31]
Basal cell carcinoma	497 (0.68)	1,861 (0.64)	0.188	1.07 [0.97–1.18]
Squamous cell carcinoma	192 (0.26)	784 (0.27)	0.841	0.98 [0.83–1.15]
Kaposi's sarcoma	21 (0.03)	55 (0.02)	0.113	1.53 [0.88–2.57]
Benign neoplasm of skin	1,361 (1.87)	6,088 (1.39)	<0.001	1.35 [1.27–1.44]

CI: confidence interval.

The results revealed several significant associations between AU and dermatological comorbidities. Inflammatory skin diseases were more prevalent in the AU group than in the control group. Notably, atopic dermatitis (19.2% vs 12.6%; $p<0.001$; odds ratio (OR) 1.65, 95% CI 1.61–1.69) and psoriasis (4.29% vs 3.26%; $p<0.001$; OR 1.33, 95% CI 1.28–1.39) exhibited significantly higher prevalence in the AU group. Furthermore, contact dermatitis, seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, pityriasis rosea, erythema multiforme, Stevens-Johnson syndrome, acne, rosacea, erythema nodosum, and hidradenitis suppurativa were more prevalent in the AU group ($p<0.001$ for all).

Infectious skin diseases also demonstrated a higher prevalence in the AU group compared with the control group. Impetigo (9.84% vs 8.23%; $p<0.001$; OR 1.22, 95% CI 1.18–1.25), cellulitis or abscess of skin (28.8% vs 22.5%; $p<0.001$; OR 1.39, 95% CI 1.37–1.42), erysipelas, dermatophytosis, candidiasis, tinea versicolor and scabies were among the infectious skin conditions with higher prevalence in the AU group ($p<0.001$ for all).

Cutaneous vasculitis had a significantly higher prevalence in the AU group compared with the control group (0.13 % vs 0.05%; $p<0.001$; OR 2.58, 95% CI 1.96–3.37). Significant associations were found between AU and systemic lupus erythematosus, discoid lupus erythematosus, systemic scleroderma, dermatomyositis, bullous pemphigoid, dermatitis herpetiformis, alopecia areata, and vitiligo ($p<0.001$ for all). Localized scleroderma and pemphigus were also more prevalent with AU, but did not reach statistical significance.

Among neoplastic skin diseases, mycosis fungoides (0.06% vs 0.04%; $p<0.001$; OR 1.45, 95% CI 1.16–1.78) and benign neoplasm of the skin (1.87% vs 1.39%; $p<0.001$; OR 1.35, 95% CI 1.27–1.44) showed a significantly higher prevalence in the AU group compared with the control group. However, no significant associations were observed for melanoma, basal and squamous cell carcinoma of the skin, or Kaposi's sarcoma.

DISCUSSION

The pathogenesis of AU is unclear. A diagnostic workup is typically only required if strongly indicated by the patient's history (4). AU is often idiopathic or spontaneous, with infections, drugs, or food allergies playing a role in only a subset of patients (1, 4, 5). Moreover, previous small studies have reported other atopic comorbidities (6) and auto-inflammatory syndromes in AU (7). The current study also confirms the association previously reported between AU and systemic lupus erythematosus (8). The higher prevalence of inflammatory skin diseases, infectious skin diseases, and organ-specific skin autoimmune diseases in the AU group suggests potential links between AU and these dermatological conditions. These findings highlight the importance of considering these comorbidities in managing AU patients to optimize treatment approaches and improve patient outcomes.

These findings prompt questions about the relationship between AU and inflammatory diseases, such as whether individuals with AU may exhibit genetic susceptibilities to inflammatory conditions or if the presence of comorbidities potentially enhances mast cell releasability, predisposing them to AU. These questions require further in-depth research. Although this study does not directly elucidate mechanistic insights, it presents valuable epidemiological data, establishing a pivotal groundwork for future research endeavours dedicated to unravelling the intricate underlying mechanisms of these associations.

Nevertheless, it is essential to acknowledge the limitations of the current study. As a retrospective cohort study, it is subject to limitations inherent in data availability and potential confounding factors. In addition, using ICD-9 codes to identify dermatological comorbidities may introduce inaccuracies or misclassification. However, the large sample size and rigorous matching process enhance the reliability and generalizability of these findings. Moreover, although the current patients were classified based on the presence of a documented AU diagnosis, it is possible that some patients initially presented with AU but progressed to chronic urticaria without a change in diagnostic coding.

Further research is necessary to establish causal relationships, elucidate underlying mechanisms, and explore optimal treatment strategies for AU patients with associated dermatological comorbidities.

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The authors have no conflicts of interest to declare.

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