METHODS FOR ASSESSING THE STAGES OF DEVELOPMENT OF CHRONIC URTICARIA: AN INTEGRATED APPROACH.

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RELEVANCE

Chronic urticaria (CU) remains a significant clinical challenge due to its unpredictable course, diverse etiologies, and profound impact on patient quality of life. In recent years, the growing prevalence of CU—estimated to affect up to 1% of the general population—has underscored the urgent need for improved diagnostic strategies [1]. Modern advances in immunology have illuminated the complex interplay of inflammatory mediators and coagulation pathways in CU, prompting the exploration of novel biomarkers such as D-dimer alongside traditional cytokine profiling (IL-6, TNF-α).

The evolving landscape of diagnostic technology, including non-invasive imaging techniques (e.g., dermoscopy) and functional tests like the basophil activation test (BAT), further emphasizes the timeliness of this research. These innovations offer the potential for earlier and more precise staging of CU, which is crucial for optimizing therapeutic approaches, particularly as targeted therapies (e.g., omalizumab) become increasingly integrated into clinical practice. Moreover, the current emphasis on personalized medicine in dermatology calls for a standardized, integrated diagnostic algorithm that can accommodate the heterogeneity of CU presentations [2]. By advancing our understanding of disease staging, clinicians can tailor treatments more effectively, reduce treatment failures, and ultimately improve long-term outcomes for patients. In summary, the relevance of assessing the stages of chronic urticaria lies in its direct implications for enhancing diagnostic accuracy, guiding individualized treatment, and reducing the overall burden of this chronic condition [3].

Keywords: Chronic urticaria, Urticaria Activity Score (UAS7), cytokine profiling, basophil activation test, dermoscopy, quality of life.

INTRODUCTION

Chronic urticaria (CU) is a heterogeneous disorder marked by recurrent hives and, occasionally, angioedema that persist for more than six weeks. Despite its prevalence, the underlying mechanisms remain only partially understood, and the clinical course is highly variable. Recent epidemiological studies estimate that CU affects 0.5–1% of the general population, with a significant impact on patient quality of life due to persistent pruritus, sleep disturbances, and psychological stress [4].

The clinical evaluation of CU has traditionally relied on patient history, physical examination, and scoring systems such as the Urticaria Activity Score over 7 days (UAS7). However, these methods do not fully capture the complexity of the disease. The integration of laboratory parameters—such as inflammatory cytokines and basophil activation markers—offers additional insight into the immunological underpinnings of CU. Moreover, the use of imaging modalities like dermoscopy and provocation tests provides further detail regarding vascular and structural changes that occur during disease progression [5].

This study was designed to assess the utility of multiple diagnostic tools for staging CU development. By correlating clinical scores with laboratory and imaging findings, we aim to develop a comprehensive diagnostic algorithm that can accurately reflect disease progression and guide treatment strategies.

MATERIALS AND METHODS

Study Design and Population - A cross-sectional observational study was conducted at the University Hospital Dermatology Clinic over an 18-month period. One hundred and fifty patients aged 18–65 years, diagnosed with chronic urticaria (defined as recurrent wheals lasting for more than six weeks), were enrolled. Exclusion criteria included acute urticaria, dermatographism without other symptoms, known autoimmune diseases, and use of systemic immunosuppressants in the previous month.

Ethical Considerations - The study protocol was approved by the Institutional Review Board (IRB) of the University Hospital. Written informed consent was obtained from all participants before enrollment.

Clinical Evaluation

Urticaria Activity Score (UAS7) - Patients were instructed to record daily occurrences of wheals and pruritus severity over a 7-day period. The UAS7 score, ranging from 0 (no symptoms) to 42 (severe symptoms), was used as the primary clinical assessment tool. Patients were categorized into three groups based on their UAS7 scores: Early Stage: UAS7 < 14; Intermediate Stage: UAS7 14–28; Advanced Stage: UAS7 > 28.

Quality of Life Assessment - The Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) was administered to assess the impact of the disease on daily living. This validated tool comprises 23 items covering emotional, symptomatic, and functional domains.

Laboratory Investigations

Inflammatory Cytokine Profiling - Venous blood samples were collected from each patient. Serum levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were quantified using enzyme-linked immunosorbent assay (ELISA) kits. Elevated cytokine levels were considered significant if they exceeded the laboratory's established reference ranges.

Basophil Activation Test (BAT) - The BAT was performed using flow cytometry to measure the expression of activation markers (CD63 and CD203c) on basophils after stimulation with anti-IgE and specific allergens. A positive BAT was defined as a significant increase in marker expression compared to unstimulated controls.

Additional Hematological and Biochemical Tests - Routine blood tests, including complete blood count (CBC) and C-reactive protein (CRP), were also conducted to assess systemic inflammation.

Imaging and Provocation Testing

Dermoscopic Examination - A subset of 50 patients underwent dermoscopic examination using a handheld dermatoscope to assess microvascular changes and skin pattern alterations associated with CU. The presence of vascular dilation, capillary loop prominence, and specific pigmentary changes were documented.

Skin Provocation Test - In the same subset, a skin provocation test was performed using histamine and cold stimuli to evaluate hyper-reactivity. The magnitude of the response was measured in terms of wheal diameter and erythema intensity.

Statistical Analysis - Data were analyzed using SPSS software (version 25.0). Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as percentages. Pearson's correlation coefficient was used to examine the relationship between

UAS7 scores and cytokine levels. Comparisons among the three disease stages were performed using one-way ANOVA with post-hoc Tukey tests. A p-value < 0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics - The study cohort consisted of 150 patients (105 females and 45 males) with a mean age of 38.7 ± 12.4 years. The duration of CU ranged from 7 months to 10 years (mean duration: 3.8 years). Based on UAS7 scores, 50 patients were classified as early-stage, 60 as intermediate-stage, and 40 as advanced-stage.

Clinical Assessment Findings - UAS7 and Quality of Life - Early-Stage Group: Mean UAS7 score of 10.2 ± 2.7; CU-Q2oL scores indicated a low impact on daily life.

Intermediate-Stage Group: Mean UAS7 score of 21.3 ± 3.5; moderate impairment in quality of life with higher emotional and functional domain scores.

Advanced-Stage Group: Mean UAS7 score of 34.5 ± 4.1; severe symptoms with significantly reduced quality of life (p < 0.001 between groups).

Laboratory Analysis - Cytokine Profiling - IL-6: Early-stage patients had mean serum levels of 3.8 ± 1.2 pg/mL, intermediate-stage patients 6.5 ± 1.7 pg/mL, and advanced-stage patients 10.2 ± 2.1 pg/mL. TNF-α: Levels were 8.4 ± 2.0 pg/mL in early-stage, 13.7 ± 3.1 pg/mL in intermediate-stage, and 19.8 ± 4.5 pg/mL in advanced-stage patients.

There was a statistically significant positive correlation between UAS7 scores and cytokine levels (IL-6: r = 0.64, p < 0.001; TNF-α: r = 0.67, p < 0.001).

Basophil Activation Test (BAT) - BAT results showed: Early Stage: 10% of patients had a positive BAT. Intermediate Stage: 45% positive BAT. Advanced Stage: 70% positive BAT.

These findings indicate that BAT positivity increases with the severity of CU.

Imaging and Provocation Test Findings - Dermoscopic Examination - In the subset of 50 patients: Early-stage patients predominantly exhibited normal vascular patterns. Intermediate-stage patients showed mild to moderate vascular dilation and increased capillary loop visibility 6. Advanced-stage patients demonstrated marked vascular abnormalities, including pronounced capillary loops and diffuse erythema.

Skin Provocation Test - The provocation tests yielded: Early Stage: Minimal response (mean wheal diameter: 2.1 ± 0.5 mm). Intermediate Stage: Moderate response (mean wheal diameter: 4.8 ± 0.9 mm). Advanced Stage: Severe hyper-reactivity (mean wheal diameter: 7.2 ± 1.2 mm).

A significant difference was observed among the groups (p < 0.001), supporting the use of provocation testing as an additional staging tool.

DISCUSSION

Integrated Assessment of Chronic Urticaria - Our study demonstrates that an integrated approach combining clinical scoring, laboratory markers, and imaging techniques significantly enhances the assessment of chronic urticaria stages. The UAS7 score remains a reliable and simple tool for initial clinical stratification, while cytokine profiling (specifically IL-6 and TNF-α) provides objective evidence of underlying inflammation. The strong correlations between UAS7 scores and cytokine levels support the hypothesis that systemic inflammation is a key driver of disease severity [7].

The Role of Basophil Activation and Provocation Testing - The increasing proportion of positive BAT results across disease stages suggests that basophil activation is closely linked to the immunological progression of CU. Although not routinely used in clinical practice due to cost and technical demands, BAT could serve as a valuable adjunct in difficult-to-treat cases or for

monitoring treatment responses [8].

Provocation tests and dermoscopic examinations further substantiate the clinical and laboratory findings by revealing microvascular alterations that parallel disease severity. The reproducible differences in wheal responses and dermoscopic patterns underscore the potential of these methods in routine diagnostics and in the evaluation of therapeutic efficacy [8].

Clinical Implications and Algorithm Proposal

Based on our findings, we propose the following diagnostic algorithm for assessing the stages of CU:

Initial Evaluation: Patient history, physical examination, and UAS7 scoring. Administer CU-Q2oL questionnaire.

Laboratory Investigations: Serum cytokine profiling (IL-6 and TNF-α).

Basophil activation test for selected cases.

Supplementary Imaging and Provocation Testing (for patients with ambiguous clinical findings or advanced disease): Dermoscopic examination to assess vascular changes. Skin provocation tests to evaluate hyper-reactivity.

This comprehensive approach enables clinicians to more accurately define the disease stage, predict progression, and tailor treatment strategies accordingly. For example, early-stage patients may benefit from conservative management and antihistamines, while advanced-stage patients might require immunomodulatory therapies or biologics.

Limitations - Despite promising results, our study has limitations. The cross-sectional design does not allow for assessment of temporal changes within the same patients. Additionally, the sample size for imaging and provocation tests was limited, and the study was conducted in a single center, potentially affecting generalizability. Future longitudinal multicenter studies are needed to validate our findings and to assess the utility of this integrated approach over time [6].

Future Directions - The integration of emerging biomarkers, such as specific autoantibodies or novel cytokine panels, may further refine CU staging. Advances in imaging technology, including high-resolution optical coherence tomography, could provide even more detailed assessments of dermal changes. Moreover, incorporating patient-reported outcomes and digital health monitoring may lead to a more dynamic and real-time evaluation of disease activity [9].

CONCLUSION

This study highlights the importance of an integrated diagnostic approach for chronic urticaria. By combining clinical scoring (UAS7), laboratory analysis (cytokine profiling and BAT), and imaging modalities (dermoscopy and skin provocation tests), clinicians can achieve a more nuanced understanding of disease progression. This multi-modal assessment not only improves diagnostic accuracy but also facilitates personalized treatment planning. Our proposed diagnostic algorithm provides a structured framework that, after further validation, may be incorporated into routine clinical practice to enhance the management of chronic urticaria.

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