

# Urticaria: An Enigmatic but Manageable Illness

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**U**rticaria, also known as hives and nettle rash, is a common skin disorder characterized by intensely pruritic wheals surrounded by erythema, often associated with subcutaneous or submucosal swelling (angioedema). It is a prevalent condition, ranging from 0.3 to 11.3%. Lifetime prevalence rates of 8.8% have been reported, with 1.8% of cases regarded as chronic. It has been estimated that approximately 10–20% of the population will experience an episode of acute urticaria at some point in their lifetime [1–3].

The etiology of urticaria is currently obscure. In most patients even extensive laboratory workup and the best clinical wisdom fail to disclose the culprit. Diagnosis is based primarily on the typical physical findings. Investigations including blood counts, chemistry, autoantibodies, complement, parasite ova, allergy skin testing (i.e., for aeroallergens or foods) and laborious imaging techniques have a very low diagnostic yield. Determining thyroid function might be helpful, since approximately 20% of patients with chronic urticaria have anti-thyroid antibodies, compared to 6% in the general population [1].

For decades, theories regarding the etiology of urticaria have been proposed but none has proven credible enough to explain the typical clinical manifestations [4]. However, a sizeable subpopulation of patients (40%–45%) have demonstrable immunoglobulin G (IgG) autoimmune antibodies directed

to the IgE-receptor  $\alpha$ -subunit, with a more severe and difficult-to-treat course. This can be assessed by the autologous serum skin test (ASST), which involves intradermal injection of the patient's own serum. A positive weal-and-flare skin reaction or in vitro basophil histamine release assay (BRA) is considered indicative of circulating autoantibodies to the high-affinity IgE receptor on dermal mast cells or blood basophils [1–4]. Unfortunately, these data have no practical advantage in devising a treatment strategy. The non-autoimmune remaining 55%–60% of patients with 'spontaneous urticaria' are still considered to be 'idiopathic' in that there is very little insight as to the cause or pathogenesis [4].

Patients with chronic urticaria (CU) experience recurrent bouts of skin rash accompanied by an unbearable itch (believed to be histamine-mediated) with swollen and disfiguring lesions. The rash interferes with daily activities, affects sleep and concentration and causes embarrassment. Furthermore, unpredictable exacerbations and dependence on medications require a change of habits and lifestyle and induce anxiety, tension and irritability. Undoubtedly, urticaria takes its toll on patients' quality of life and mental condition. The disfigurement and discomfort-associated CU often poses a serious challenge to the treating clinician, and long-term hardships for patients and their families [5]. A recent meta-analysis confirmed the association between psychological factors and chronic urticaria [6]. This meta-analysis shows a positive correlation between CU and markers of poor psychological wellness, indicating that psychotherapeutic treatments and behavioral interventions may prove beneficial.

Treating chronic urticaria is extremely frustrating for most practicing physicians. Except for the second-generation non-sedat-

ing antihistamines, the major achievements in the last few decades were an improved classification of the clinical phenotypes, the provision of safer symptomatic treatments, and avoidance of long-term corticosteroid use. Very recently, however, immunomodulating and disease-modifying drugs (i.e., cyclosporine, methotrexate, mycophenolate, omalizumab) have been offered for chronic refractory cases [1]. In a recent meta-analysis omalizumab (Xolair<sup>®</sup>, Genentech, Inc. and Novartis Pharmaceuticals Corporation, USA) was found to be safe and efficacious in seven randomized controlled studies comprising 1312 patients with CSU, as compared to placebo [7]. However, data on the duration of effective treatment with omalizumab, and head-to-head studies against conventional (and less expensive) therapy are not currently available.

In the last 25 years new clinical parameters and evaluation instruments were developed to assess the impact of urticaria on quality of life (QoL) and subjective outcomes that can be recorded by the patients [8]. Suggested patient-reported outcomes (PROs) in urticaria refer to general health-related reports, such as illness perception, health-related quality of life (HRQoL), symptom severity, disease activity scores, satisfaction, wellbeing, perceived disease control, etc. Nonetheless, PROs are already integrated in clinical research and are used by regulatory bodies due to their relevance in the overall assessment of treatment efficacy. They can also provide clinically important endpoints for research and disease management plans.

In light of this, the efforts of Kessel and team [9] in adopting and validating a Hebrew version of the Chronic Urticaria Quality-of-life Questionnaire (CU-Q2oL) are to be commended. This questionnaire, originally developed and validated in Italy

by Biardini et al. [10,11], has undergone validation and cross-cultural confirmation and was already introduced into clinical practice in other countries (Germany, Spain, Turkey and Poland). Despite the limitations of the study (i.e., small sample group, short follow-up period), Kessel et al. have demonstrated that the Israeli version of the CU-Q2oL is a reliable and valid instrument and can be used to assess chronic urticaria patients.

It is hoped that despite its enigmatic mechanism and lack of a definitive panacea, urticaria will be better managed in Israel by using standardized tools that can guide physicians in follow-up and clinical decision making.

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