

Chronic Idiopathic Urticaria

A "Cinderella" Disease With a Negative Impact on Quality of Life and Health Care Costs

CHRONIC IDIOPATHIC URTICARIA (CIU) is defined as the daily or almost daily occurrence of spontaneous pruritic wheals for at least 6 weeks.¹ Although good epidemiological data are lacking, the prevalence in an outpatient dermatology clinic is around 4%.² Angioedema is associated with CIU in about 40% of cases³ and, although it causes serious distress and disability, is hardly ever fatal. Physical urticarias such as symptomatic dermatographism and delayed pressure urticaria frequently occur concurrently with CIU.

Chronic idiopathic urticaria is positively associated with autoimmune thyroid disease⁴ and itself has an autoimmune basis in 30% to 50% of white patients⁵⁻⁷ owing to the presence of functional IgG autoantibodies reactive with the α chain of the high-affinity IgE receptor Fc ϵ R1 or, less commonly, against IgE. These patients are recognized by the autologous serum skin test results⁸; confirmation of the diagnosis requires in vitro demonstration of histamine-releasing activity by the patient's serum against basophil leukocytes from a healthy donor. Alternatively, basophils from a rat basophil leukemia cell line can be used as indicator cells.⁹ Recently, the ability

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of serum to evoke expression of CD203c on basophil leukocytes in vitro has been proposed as a screening test for autoimmune urticaria,¹⁰ but the specificity and sensitivity of this test need to be established. Confirmation of an autoimmune basis for a patient's urticaria is important in disease investigation and treatment; a positive result obviates the necessity for further investigations and may provide a basis for immunotherapy in selected patients.¹¹

In at least 50% of patients with CIU, the rash is truly idiopathic.¹² A defect of signal transduction has been identified in the basophil leukocytes of some of these patients,¹³ but the defect's significance remains to be established. Chronic infections such as *Helicobacter pylori* gastritis are rarely if ever significant. A role for dietary factors ("pseudoallergens") has been proposed but requires substantiation in each case by rigorous placebo-controlled challenge testing.¹⁴

The prognosis is for chronicity; a follow-up study¹⁵ of 554 patients yielded an average figure for disease remission in 5 years of 70%.

Exacerbations of CIU are triggered by aspirin, other nonsteroidal anti-inflammatory drugs, alcohol, over-

tiredness, and stress, and all patients should be advised appropriately. H₁ antihistamines are the mainstay of symptomatic treatment. Low-sedation antihistamines can, if necessary, be given safely in an off-label dosage¹⁶ and may also be supplemented by a sedative antihistamine at night, when pruritus is often the most troublesome.¹⁷ If the latter is prescribed, the patient should be advised that impaired cognitive function may persist throughout the following day. Doxepin hydrochloride, a tricyclic antidepressant with potent H₁ antihistaminic properties, is also valuable in patients with nocturnal exacerbations but should be administered cautiously, especially in the elderly and those with cardiovascular disease. The value of additional treatment by antileukotrienes such as montelukast sodium remains to be established¹⁸ but, in the authors' experience, it is of limited value. Immunotherapy with cyclosporine, usually prescribed for only 1 to 3 months, is of established benefit in selected patients with autoimmune urticaria¹¹ but may also be effective in patients with recalcitrant CIU in whom there is no evidence of an autoimmune basis.

That there remains a host of anecdotal remedies in addition to the foregoing well-recognized and generally well-established therapeutic options is a testament to the lack of investigational effort worldwide in the pathomechanisms of urticaria, its investigation, and its evidence-based management. This is especially unfortunate because chronic urticaria is a recognized "heart sink" dermatosis causing serious impairment of quality of life. O'Donnell et al¹⁹ studied 142 adult patients with CIU by using an internationally recognized quality-of-life instrument. The study showed that the degree of occupational social and personal disability and handicap in these patients, mainly due to pruritus, was comparable to that of patients with severe coronary artery disease. Given that chronic urticaria affects an estimated 1% of the population,²⁰ a case can be made for greatly increased resource allocation for research into the etiology, epidemiology, investigation, and treatment of this common and distressing disease. This case could be further strengthened by data on the direct and indirect health care costs of patients with chronic urticaria.

The article by DeLong et al,²¹ from The Johns Hopkins University allergy and immunology clinics, in this month's issue of the *Archives* is therefore especially timely. These authors studied 50 adult patients with CIU who had been treated conventionally with H₁ antihistamines but without systemic corticosteroids or other immunosuppressants during the month prior to the study. They measured 4 direct health care costs

(laboratory workup, medication usage, and outpatient and emergency department visits), and 2 indirect costs (earnings lost because of travel time and absenteeism from work). For this predominantly outpatient chronic disorder, the mean primary direct annual cost of \$1280 was for medications (principally, nonsedating H₁ antihistamines); the mean annual cost of outpatient and emergency department visits was \$148 and for laboratory tests was \$17. An additional mean annual loss-of-earnings cost of \$322 yielded an average total yearly cost of \$2047. Analysis of costs by sex indicated that women incurred higher direct and indirect health care costs and that, not surprisingly, costs rose in proportion to disease severity.

This study almost certainly underestimates the actual direct and indirect costs of chronic urticaria because those taking additional medications, including immunosuppressants, were excluded. It would also have been of interest to have segregated those patients with autoimmune urticaria as defined by the results of autologous serum skin testing and serum histamine-releasing activity, because disease in patients in this subgroup is likely to run a more severe and protracted course.²² However, we believe that a strong case, based on economic costs as well as the degree of handicap and impaired quality of life, can be made for greater resource allocation for research, as well as for disease investigation and management in patients with chronic urticaria.

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