Original Article

Dissociation Between History and Challenge in Patients with Physical Urticaria

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What is already known about this topic? Physical urticaria is a subtype of chronic urticaria that is induced by a physical stimulus.

What does this article add to our knowledge? In a study of patients referred for evaluation of physical urticaria, more than one-third of the subjects had consistently negative results to the presumed physical stimulus reported by history to provoke urticaria.

How does this study impact current management guidelines? Physicians who do not perform testing may wish to consider referral to a specialty clinic or tertiary care center for evaluation.

BACKGROUND: Physical urticaria is a subtype of chronic urticaria induced by a physical stimulus.
OBJECTIVE: To evaluate the consistency between a history of physical urticaria and results of challenge testing.
METHODS: Seventy-six subjects, ages 3 to 77 years old, were referred with the diagnosis of a physical urticaria and were evaluated by using challenge testing directed toward the presenting diagnosis, yet included other stimuli based on history. The majority of subjects were tested to 3 or more stimuli, thus 294 provocation tests were performed. Fifty-seven subjects were surveyed for the status of their physical urticaria at least 1 year after initial evaluation.
RESULTS: Of the 76 subjects with a positive history of a physical urticaria, 38% (n = 29) were challenge negative to the presenting diagnosis. Eight subjects within the challenge negative group reacted positively to additional testing, thus 28% (n = 21) remained negative to all challenge testing, which allowed discontinuation of medications and avoidance behavior. A negative challenge result was less likely with subjects who presented with cold-induced urticaria (25%), delayed pressure urticaria (25%), and dermatographism (29%), yet more common with cholinergic (65%) and solar urticaria (67%). A 1-year follow-up survey of 57 subjects was consistent with initial results. Nineteen of this subgroup were rechallenged for the presenting diagnosis, and the outcome was unchanged in 17 subjects and, in 2 subjects the urticaria had resolved.
CONCLUSIONS: The diagnosis by history of a physical urticaria should be verified by testing whenever possible and particularly if the condition is judged as severe and thus requires both significant life-style changes and pharmacologic intervention. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:786-90)

Key words: *Urticaria; Physical urticaria; Challenge testing; Cold; Cholinergic; Dermatographism; Delayed pressure*

Physical urticaria is a unique form of hives that is induced by specific physical stimuli. It is estimated that 0.5% of the population has physically induced urticaria and/or angioedema and that this population comprises 20% to 30% of all cases of chronic urticaria (CU).[1,2] The lifetime prevalence of a physical urticaria is estimated to be 4% to 6%.[1] Disease resolution is quite variable, depending on the subtype of physical urticaria, age of onset, and severity but has been estimated at 13% to 16% after 1 year and 50% after 5 years.[3,4] The pathogenesis of physical urticaria is associated with the release of mediators from cutaneous mast cells, but the mechanisms that underlie this mast cell activation remain unclear.[5,6] The various forms of physical urticaria, their relevant stimuli, and prevalence include the following: dermatographism (overall prevalence, 2%-5%; 10% of CU), cold urticaria (2% of CU), delayed pressure urticaria and/or angioedema (1%-2% of CU), cholinergic urticaria (11% of young adults, 2%-5% of CU),

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Abbreviations used
CU- Chronic urticaria
IQR- Interquartile range

exercise-induced urticaria, local heat urticaria (0.2% of CU), vibratory urticaria (0.1% of CU), solar urticaria (0.4%-0.5% of CU), and aquagenic urticaria (0.3 % of CU).[1,3,7-12] The diagnosis is based on a history of episodic physically induced urticaria ideally confirmed by the reproduction of this response after office-based provocation testing.[13,14] However, challenge testing requires proper equipment, training, and clinical support. Because of these requirements, caregivers may rely on the patient history for diagnosis and selection of intervention strategies. We thus ask the question as to how often the history would not be reproduced if challenge testing were performed.

In our study, we performed at total of 294 challenge tests prospectively on a cohort of 76 subjects who were diagnosed by a referring physician with a physical urticaria. Most subjects were on medications and had altered their lifestyle to avoid reactions. Challenge testing was directed by the presenting diagnosis and the clinical history. As will be shown, our study revealed that a significant portion of our subjects referred with the diagnosis of a specific physical urticaria had negative results to challenge, and these findings remained consistent on follow-up at least 1 year later.

METHODS

Subjects

A cohort of 76 subjects, ages 3 to 77 years, diagnosed with a physically induced urticaria by an internist, pediatrician, allergist, or dermatologist, were referred to the National Institutes of Health from 2009 to 2014 under protocol 09-I-0126 (Pathogenesis of Physical Induced Urticarial Syndromes) for further evaluation. At least 1 week before evaluation, all the subjects refrained from taking antihistamines and antileukotrienes or any agent that could affect the outcome of challenge testing. After informed consent, all the subjects underwent a thorough history, which included a 36-question clinical survey of physical urticaria administered by clinical staff (see Appendix E1 in this article's Online Repository at www.jaci-inpractice.org) and a physical examination. The subjects were acclimated to the ambient challenge room temperature for at least 2 hours before testing.

Challenge testing

Challenge testing was directed toward the presenting diagnosis (eg, cold urticaria), yet included other stimuli based on the history and survey results (Table I). For example, 1 subject was referred for the evaluation of cold urticaria while skiing. On questioning, the subject reported the development of hives on non−cold exposed areas and after jogging in the cold. This subject was tested for cold-induced urticaria and cholinergic and/or exercise-induced urticaria. All the subjects were tested for dermatographism, and the majority of subjects were challenged to 3 or more other physical stimuli (median, 4.0; interquartile range [IQR], 1.0). Standard challenge testing was performed as described (Table I)[2,9,13] and included the following:

- Dermatographism: stroking of skin at various pressures (20-144 g/m^2) by using a dermographometer
- Cold-induced urticaria: stimulation by using a 50-mL glass beaker of ice water (0°C-2°C) placed on the forearm for 1 to 10 minutes; cold hand water submersion (10°C) to 2 inches above the wrist for 5 minutes; and, in some cases, total body cold exposure (4°C) for 10 to 20 minutes; evaporative cooling of water droplet with airflow at approximately 1 L/s
- Cholinergic urticaria and/or exercise induced: 15- to 25-minute treadmill exercise challenge until there was profuse sweating and continued exercise for ≥10 minutes, and/or 20 to 30 minutes hot water bath (40°C) until a ≥1°C rise in core body temperature was documented

TABLE I. Features and testing of physical urticaria

	Distinguishing features	Diagnostic testing*
Dermatographism	Linear, pruritic hives from shear force, most common physical urticaria	Linear stroking at various pressures (20-144 g/m^2) by using a dermatographometer, FricTest (Moxie GmbH, Berlin, Germany), or ballpoint pen
Cold	Pruritic wheal and flare from cold contact, up to a third of cases of physical urticaria	Ice water in a 50-mL beaker, placement for 1-10 min, cold hand immersion for 5 min, total body cold exposure, evaporative cooling
Cholinergic	Pinpoint diffuse papular lesions from an increase in core body temperature	Exercise challenge to induce sweat plus ≥10 min, or passive warming by using a hot water bath to raise body temperature >1°C
Exercise induced	Not induced by passive warming, larger lesions often are associated with systemic symptoms	Exercise challenge as above
Delayed pressure	Pruritus, swelling, and pain 4-8 h after exposure, may be associated with systemic symptoms of fatigue, arthralgia	100 g/m^2 of pressure for 5-180 s duration on the forearm by using a dermatographometer and 15 lb (6.8 kg) weight bearing on shoulder or lower leg for 15-20 min
Solar	Immediate reaction to UV and visible light, resolves within 24 h, distinguish from polymorphous light eruption	UV-A, UV-B, and visible light stimulation of variable intensity to establish minimal urticarial dose
Vibratory	Erythema and swelling beyond provocation site	Vortex vibratory stimulation for 4 min at 2500 rpm
Local heat	Rare, reaction limited to area of exposure	Hot water (45°C-50°C) in glass beaker placement 1-10 min to establish threshold
Aquagenic	Rare, distinguish from evaporative cooling and cold urticaria	Submersion of hand and/or forearm at approximately 35° and application of wet compress for 20-30 min

*Based on Refs 2, 9, 13.

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