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Provocation tests in cholinergic urticaria: unmet needs

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Dear Editor,

Urticaria is a skin disease defined by the development of hives, angioedema, or both. Hives are erythematous, edematous lesions of variable size, characterized by intense itching, which occur in reaction to vasodilation and increased vascular permeability in the superficial dermis. They are fleeting, with the skin returning to normal appearance within 30 minutes to 24 hours, without leaving any residual lesions. Angioedema presents as sudden, marked edema of the deep dermis, subcutaneous tissue, or mucous membranes, characterized by pain and a burning sensation rather than itching, and resolving gradually within 72 hours.

Depending on the duration of its clinical manifestations, urticaria is classified as acute (less than 6 weeks) or chronic (greater than or equal to 6 weeks). Chronic urticaria can occur spontaneously or be induced by specific stimuli, which are diagnosed through provocation tests with external triggers.

Chronic inducible urticarias (CIndUs) can be subdivided according to the triggering external stimulus as physical (dermographism, delayed pressure urticaria, cold-, heat-, solar and vibratory urticaria) or non-physical (adrenergic, contact, aquagenic, and cholinergic urticaria). Cholinergic urticaria (CholU) is triggered by a systemic increase in body temperature with consequent sweating—unlike some of its differential diagnoses, such as heat urticaria (HU), which has localized external heat as its primary trigger, or solar urticaria (SU), which is due to exposure to UVA, UVB, or visible light.

CholU was first described by Duke in 1924 and is characterized by the onset of highly pruritic or painful micropapular lesions with surrounding erythema in the context of increased core body temperature as a result of physical exercise, hot baths, emotional stress, or intake of spicy foods or hot beverages. The lesions of CholU are approximately 1 to 3 mm in size and can occur anywhere on the body, except the palmoplantar and axillary regions. Nevertheless, they mainly affect the trunk and upper limbs. These small papules may coalesce to form large wheals. Symptoms are usually rapidly evanescent, lasting no more than 1 hour. They may worsen with higher ambient temperatures, although some patients report the onset of lesions even in low-temperature environments, especially during physical activity.

CholU is incident and prevalent predominantly between the second and third decades of life. There is no difference in prevalence between males and females. Some studies suggest an estimated overall prevalence of 4.1–11.2% in the general population.

A study with 111 participants sought to characterize the unmet medical needs of patients regarding assessment and follow-up of CholU in German-speaking countries. The authors conducted an online survey on symptoms, delay in diagnosis, impact on activities of daily living, quality of life, and experience of medical care. Although virtually all patients reported typical signs and symptoms of CholU, they reported a significant diagnostic delay of 30.2 months (range 0 to 279 months). Only 16% underwent provocation testing, demonstrating the lack of practical diagnostic tests. Ninety percent of patients reported having uncontrolled disease, resulting in severe impact on their everyday activities, sleep, and quality of life. This study reveals a pressing need for improvements in the diagnostic workup and care of patients with this condition, as well as better treatment options.[1]

The etiology of each CholU subtype is gradually being investigated and elucidated, but its overall pathophysiology is still not fully understood. It is believed to involve acetylcholine, pore occlusion, the M3 cholinergic receptor (CHRM3), allergy to sweat components, serum inflammatory factors, and dyshidrosis, and each CholU subtype has been suggested to involve different or mixed causes. Despite numerous gaps in the proposed pathophysiology of CholU, four subtypes have been proposed: type I, CholU with sweat allergy; type II, follicular-

type CholU; type III, CholU with palpebral angioedema (CholU-PA); and type IV, CholU with acquired anhidrosis and/or hypohidrosis.[2] Histamine is a mediator involved in a similar manner in all reported CholU subtypes.

Unlike in other types of urticaria, many patients with CholU complain of paresthesias, which have a major impact on quality of life. CholU is a disease that drastically alters the individual's concept of biopsychosocial well-being, as it markedly reduces quality of life, favors indiscriminate self-medication, and predisposes to absenteeism. CholU is incident and prevalent predominantly between the second and third decades of life. Lesions tend to last 15 to 60 minutes and may be associated with local angioedema. When CholU is suspected, it is essential to distinguish it from exercise-induced anaphylaxis, aquagenic urticaria, cold-induced CholU, HU, and SU.[1-2]

Provocation testing to confirm CholU also aims to rule out the diagnosis of exercise-induced anaphylaxis. Caution should be exercised when performing this test on individuals with heart disease and in patients with presentations other than the classical skin lesions. It is generally agreed that an increase in body temperature above 1 °C from baseline, as indicated by a passive warming test (sitting for ≤ 15 min in a 42 °C water bath), confirms the diagnosis of CholU.[2]

A standardized protocol has been proposed to diagnose and measure CholU thresholds, using a cycle ergometer with heart rate and temperature monitoring. The test is performed by ergometry with heart rate control. The patient mounts the cycle ergometer and starts pedaling, after being instructed that the pulse should rise by 15 bpm every 5 minutes, reaching 90 bpm above baseline within 30 minutes. Body temperature is also measured throughout the test. The time to onset of urticaria is inversely proportional to disease severity, i.e., the sooner lesions appear, the more severe the patient's CholU.[3]

CholU is extremely detrimental to the biopsychosocial well-being of affected individuals, and provocation tests and other diagnostic tools that can be easily reproduced in settings outside specialist referral centers are still lacking. There is a pressing need for novel low-cost, low-tech, safe techniques with good reproducibility that can supplement diagnosis by specialist physicians in private outpatient clinics or in primary health care, especially in the context of the Unified Health System and in other developing countries.

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